

ORGANIC Synthesis

THIRD EDITION

MICHAEL B. SMITH

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MICHAEL B. SMITH UNIVERSITY OF CONNECTICUT

ORGANIC SYNTHESIS, Third EDITION

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About the Author

PROFESSOR MICHAEL B. SMITH was born in Detroit, Michigan in 1946 and moved to Madison Heights, Virginia in 1957, where he attended high school. He received an A.A. from Ferrum College in 1967 and a B.S. in chemistry from Virginia Polytechnic Institute in 1969. After working for three years at the Newport News Shipbuilding and Dry Dock Co. in Newport News VA as an analytical chemist, he entered graduate school at Purdue University. He received a Ph.D. in Organic chemistry in 1977, under the auspices of Professor Joe Wolinsky. Professor Smith spent one year as a faculty research associate at the Arizona State University with Professor G. Robert Pettit, working on the isolation of cytotoxic principles from plants and sponges. He spent a second year of postdoctoral work with Professor Sidney M. Hecht at the Massachusetts Institute of Technology, working on the synthesis of bleomycin A2. Professor Smith moved to the University of Connecticut in 1979, where he is currently professor of chemistry. In 1986 he spent a sabbatical leave in the laboratories of Professor Leon Ghosez, at the Université Catholique de Louvain in Louvain-la-Neuve, Belgium, as a visiting professor.

Professor Smith's research interests focus on (1) the synthesis and structure-proof of bioactive lipids obtained from the human dental pathogen *Porphyromonas gingivalis*. The initial work will be extended to study the structure-biological activity relationships of these compounds. (2) A systematic study of the influence of conductivity-enhancing dopants on conducting polymers, and a green-chemistry study of chemical reactions mediated by conducting polymers in a neutral, two-phase system. (3) The development of chemical probes that targets and allows fluorescent imaging of cancerous hypoxic tumors.

In addition to this research, Professor Smith is the author of the 5th and 6th editions of *March's Advanced Organic Chemistry* and editor of the *Compendium of Organic Synthetic Methods*, Volumes 6-12. He is the author of *Organic Chemistry: Two Semesters*, in it's second edition, which is an outline of undergraduate organic chemistry to be used as a study guide for the first organic course. He has authored a research monograph entitled *Synthesis of Non-alpha Amino Acids*. He is also the author of an undergraduate textbook in organic chemistry entitled *Organic Chemistry. An Acid-Base Approach*.

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Preface to the 3rd edition

The new edition of *Organic Synthesis* has been revised and rewritten from front to back. I want to thank all who used the book in its first and second editions. The book has been out of print for several years, but the collaboration of Warren Hehre and Wavefunction, Inc. made the third edition possible. It is the same graduate level textbook past users are familiar with, with two major exceptions. First, the book has been revised and updated. Second, molecular modeling problems are included in a manner that is not obtrusive to the theme of understanding reactions and synthesis. More than 60 molecular modeling problems are incorporated into various discussions, spread throughout 11 of the 13 reactions-synthesis oriented chapters. These are intended for the *SpartanModel* program, which can be purchased from Wavefunction. *SpartanModel* will allow the reader to manipulate each model and, in most cases, change or create model compounds of interest to the reader. It is our belief that the selected molecular modeling problems will offer new insights into certain aspects of chemical reactivity, confirmational analysis, and stereoselectivity.

Updated examples are used throughout the new edition when possible, and new material is added that make this edition reflect current synthetic methodology. The text has been modified in countless places to improve readability and pedagogy. This new edition contains references taken from more than 6100 journal articles, books, and monographs. Of these references, more than 950 are new to this edition, all taken from the literature after 2002. More than 600 updated or new reactions have been added. There are several entirely new sections that discuss topics missing from the 2^{nd} edition. These include $S_N 2$ type reactions with epoxides; the Burgess Reagent; functional group rearrangements (Beckmann, Schmidt, Curtius, Hofmann, Lossen); Oxidation of allylic carbon with ruthenium compounds; A comparison of LUMO-mapping with the Cram model and Felkin-Anh models in chapter 4; Electrocyclic reactions; [2.3]-sigmatropic rearrangement (Wittig rearrangement); consolidation of C–C bond forming reactions of carbocations and nucleophiles into a new section.

Homework in each chapter has been extensively revised. There are more than 800 homework problems, and more than 300 of the homework problems are new. Most of the homework problems do not contain leading references for the answers. The answers to all problems from chapters 1-9, and 11-13 are available in an on-line *Student Solutions Manual* for this book. As in previous edition, a few leading references are provided for the synthesis problems in chapter 10. Although answers are given for homework that relates to all other chapters, in chapter 10 most problems do not have answers. The student is encouraged to discuss any synthetic problem with their instructor.

With the exception of scanned figures, all drawings in this book were prepared using ChemDraw, provided by CambridgeSoft, and all 3D graphics are rendered with Spartan, provided by Wavefunction, Inc. I thank both organizations for providing the software that made this project possible.

I express my gratitude to all of those who were kind enough to go through the first and second editions and supply me with comments, corrections, and suggestions.

For this new edition, special thanks and gratitude are given to Warren Hehre. Not only did he design the molecular modeling problems, but provided the solutions to the problems and the software. Warren also helped me think about certain aspects of organic synthesis in a different way because of the modeling, and I believe this has greatly improved the book and the approaches presented in the book. Special thanks are also given to Ms. Pamela Ohsan, who converted the entire book into publishable form. Without her extraordinary efforts, this third edition would not be possible.

Finally, I thank my students, who have provided the inspiration over the years for this book. They have also been my best sounding board, allowing me to test new ideas and organize the text as it now appears. I thank my friends and colleagues who have provided countless suggestions and encouragement over the years, particularly Spencer Knapp (Rutgers), George Majetich (Georgia), Frederick Luzzio (Louisville), and Phil Garner (Washington State). You have all helped more than you can possibly know, and I am most grateful.

A special thanks to my wife Sarah and son Steven, whose patience and understanding made the work possible.

If there are errors, corrections, and suggestions, please let me know by Email or normal post. Any errors will be posted at http://www.elsevierdirect.com/companions/9781890661403.

Thank you again. I hope this new edition is useful to you in your studies.

Michael B. Smith Storrs, Connecticut April, 2010

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Preface to the 1st edition. Why I wrote this book!

A reactions oriented course is a staple of most graduate organic programs, and synthesis is taught either as a part of that course or as a special topic. Ideally, the incoming student is an organic major, who has a good working knowledge of basic reactions, stereochemistry and conformational principles. In fact, however, many (often most) of the students in a first year graduate level organic course have deficiencies in their undergraduate work, are not organic majors and are not synthetically inclined. Does one simply tell the student to "go away and read about it," giving a list of references, or does one take class time to fill in the deficits? The first option works well for highly motivated students with a good background, less well for those with a modest background. In many cases, the students spend so much time catching up that it is difficult to focus them on the cutting edge material we all want to teach. If one exercises the second option of filling in all the deficits, one never gets to the cutting edge material. This is especially punishing to the outstanding students and to the organic majors. a compromise would provide the student with a reliable and readily available source for background material that could be used as needed. The instructor could then feel comfortable that the proper foundations have been laid and push on to more interesting areas of organic chemistry.

Unfortunately, such a source of background material either is lacking altogether or consists of several books and dozens of review articles. I believe my teaching experience at UConn as just described is rather typical, with a mix of non-organic majors, outstanding and well-motivated students, and many students with weak backgrounds who have the potential to go on to useful and productive careers if time is taken to help them. Over the years I have assigned what books were available in an attempt to address these problems, but found that "graduate level textbooks" left much to be desired. I assembled a large reading list and mountains of handouts and spent half of my life making up problems that would give my students a reasonable chance at practicing the principles we were discussing. I came to the conclusion that a single textbook was needed that would give me the flexibility I craved to present the course I wanted to teach, but yet would give the students the background they needed to succeed. As I tried different things in the classroom, I solicited the opinions of the graduate students who took the course and tried to develop an approach that worked for them and allowed me to present the information I wanted. The result is this book. I hope that it is readable, provides background information, and also provides the research oriented information that is important for graduate organic students. I also hope it will be of benefit to instructors who face the same challenges I do. I hope this book will be a useful tool to the synthetic community and to graduate level education.

From talks with many people I know that courses for which this book is targeted can be for either one or two semesters. The course can focus only on functional groups, only on making carbon-carbon bonds, on some combination of both (like my course), or only on synthesis.

I have tried to organize the book in such a way that one is not a slave to its organization. Every chapter is internally cross-referenced. If the course is to focus upon making carboncarbon bonds, for example, there are unavoidable references to oxidation reagents, reducing agents, stereochemical principles, etc. When such a reaction or principle appears, the section and chapter where it is discussed elsewhere in the book is given "in line" so the student can easily find it. It is impossible to write each chapter so it will stand alone, but the chapters are reasonably independent in their presentations. I have organized the book so that functional groups are discussed in the first few chapters and carbon-carbon bond formation reactions are discussed in later chapters, making it easier to use the one book for two different courses or for a combination course. The middle chapters are used for review and to help the student make the transitions from functional group manipulations to applying reactions and principles and thence to actually building molecules. I believe that a course devoted to making carboncarbon bonds could begin with chapter 8, knowing that all pertinent peripheral material is in the book and readily available to the student. The ultimate goal of the book is to cut down on the mountains of handouts, provide homework to give the student proper practice, give many literature citations to tell the student exactly where to find more information, and allow the instructor to devote time to their particular focus.

This book obviously encompasses a wide range of organic chemistry. Is there a theme? Should there be? The beautiful and elegant total syntheses of interesting and important molecules published by synthetic organic chemists inspired me to become an organic chemist, and I believe that synthesis focuses attention on the problems of organic chemistry in a unique way. To solve a synthetic problem, all elements of organic chemistry must be brought to bear: reactions, mechanism, stereochemistry, conformational control, and strategy. Synthesis therefore brings a perspective on all aspects of organic chemistry and provides a theme for understanding it. The theme of this book is therefore the presentation of reactions in the context of organic synthesis. Wherever possible, examples of a given reaction, process, or strategy are taken from a published total synthesis. The disconnection approach is presented in the first chapter, and as each new functional group transform and carbon-carbon bond forming reaction is discussed, the retrosynthetic analysis (the disconnect products for that reaction) is given. An entire chapter (chapter 10) is devoted to synthetic strategies, and chapter 14 provides examples of first year students' first syntheses. I believe that this theme is a reasonable and useful device for presenting advanced organic chemistry.

The text is fully referenced to facilitate further study, and (where feasible) the principal researcher who did the work is mentioned by name, so the student can follow that person's work in the literature and gain even more insight into a given area. As far as it is known to me, the pioneering work of the great chemists of the past has been referenced. Many of the "named reactions" are no longer referenced in journals, but when they are first mentioned in this book, the original references are given. I believe the early work should not be lost to a new generation of students.

In many cases I have used 3-D drawings to help illustrate stereochemical arguments for a given process. I give the structure of each reagent cited in the text, where that reagent is mentioned, so a beginning student does not have to stop and figure it out. This is probably unnecessary for many students, but it is there if needed.

This is a reaction oriented book, but an attempt is made to give brief mechanistic discussions when appropriate. In addition, some physical organic chemistry is included to try to answer the obvious if unasked questions: why does that alkyl group move, why does that bond break, why is that steric interaction greater than the other one, or why is that reaction diastereoselective?

Most of all, a student needs to practice. Chapters 1-13 have end-of chapter problems that range from those requiring simple answers based on statements within the text to complex problems taken from research literature. In a large number of cases literature citations are provided so answers can be found.

The first part of the book (chapters 1-4) is a review of functional group transforms and basic principles: retrosynthesis, stereochemistry, and conformations. Basic organic reactions are covered, including substitution reactions, addition reactions, elimination reactions, acid/base chemistry, oxidation and reduction. The first two chapters are very loosely organized along the lines of an undergraduate book for presenting the functional group reactions (basic principles, substitution, elimination, addition, acyl addition, aromatic chemistry). Chapter 1 begins with the disconnection approach. I have found that this focuses the students' attention on which reactions they can actually apply and instantly shows them why it is important to have a larger arsenal of reactions to solve a synthetic problem. This has been better than any other device I have tried and that is why it is placed first. Most of the students I see come into our program deficient in their understanding of stereochemistry and conformational control, and so those topics are presented next. Some of this information is remedial material and where unneeded can be skipped, but it is there for those who need it (even if they will not admit that they do). Chapter 2 presents a mini-review of undergraduate organic chemistry reactions and also introduces some modern reactions and applications. Chapter 3 is on oxidation and chapter 4 is on reduction. Each chapter covers areas that are woefully under-emphasized in undergraduate textbooks.

Chapter 5 covers hydroboration, an area that is discussed in several books and reviews. I thought it useful to combine this material into a tightly focused presentation which (1) introduces several novel functional group transforms that appear nowhere else and (2) gives a useful review of many topics introduced in chapters 1-4. Chapter 6 reviews the basic principles that chemists use to control a reaction rather than be controlled by it. It shows the techniques chemists use to "fix" the stereochemistry, if possible, when the reaction does not do what it is supposed to. It shows how stereochemical principles guide a synthesis. An alternative would be to separate stereochemistry into a chapter that discusses all stereochemical principles. However, the theme is synthesis, and stereochemical considerations are as important a part of a synthesis as the reagents being chosen. For that reason, stereochemistry is presented with the reactions

in each chapter. Chapter 6 simply ties together the basic principles. This chapter also includes the basics of ring-forming reactions. Chapter 7 completes the first part of the book and gives a brief overview of what protecting groups are and when to use them.

The last half of the book focuses on making carbon-carbon bonds. It is organized fundamentally by the disconnection approach. In Chapter 1, breaking a carbon-carbon bond generated a disconnect product that was labeled as C^d (a nucleophilic species), C^a (an electrophilic species), or C^{radical} (a radical intermediate). In some cases, multiple bonds were disconnected, and many of these disconnections involved pericyclic reactions to reassemble the target. the nucleophilic regents that are equivalent to C^d disconnect products are covered in Chapters 8 and 9, with the very important enolate anion chemistry separated into Chapter 9. Chapter 10 presents various synthetic strategies that a student may apply to a given synthetic problem. This information needs to be introduced as soon as possible, but until the student "knows some chemistry", it cannot really be applied. Placement of synthetic strategies after functional group transforms and nucleophilic methods for making carbon-carbon bonds is a reasonable compromise. Chapter 11 introduces the important Diels-Alder cyclization, as well as dipolar cycloadditions and sigmatropic rearrangements that are critically important to synthesis. Chapter 12 explores electrophilic carbons (C^a), including organometallics that generally react with nucleophilic species. Chapter 13 introduces radical and carbene chemistry. Chapter 14 is included to give the student a taste of a first time student proposal and some of the common mistakes. The point is not to reiterate the chemistry but to show how strategic shortsightedness, poor drawings, and deficiencies in overall presentation can influence how the proposal is viewed. It is mainly intended to show some common mistakes and also some good things to do in presenting a synthesis. It is not meant to supersede the detailed discussions of how and why a completed elegant synthesis is done but to assist the first-time student in preparing a proposal.

The goal of this work is to produce a graduate level textbook, and it does not assume that a student should already know the information, *before* the course. I hope that it will be useful to students and to the synthetic community. Every effort has been made to keep the manuscript error-free. Where there are errors, I take full responsibility and encourage those who find them to contact me directly, at the address given below, with corrections. Suggestions for improving the text, including additions and general comments about the book are also welcome. My goal is to incorporate such changes in future editions of this work. If anyone wishes to contribute homework problems to future editions, please send them to me and I will, of course, give full credit for any I use.

I must begin my "thank yous" with the graduate students at UConn, who inspired this work and worked with me through several years to develop the pedagogy of the text. I must also thank Dr. Chris Lipinski and Dr. David Burnett of Pfizer Central Research (Groton, CT) who organized a reactions/synthesis course for their research assistants. This allowed me to test this book upon an "outside" and highly trained audience. I am indebted to them for their suggestions and their help.

There are many other people to thank. Professor Janet Carlson (Macalester College) reviewed a primeval version of this book and made many useful comments. Professors Al Sneden and Suzanne Ruder (Virginia Commonwealth University) classroom tested an early version of this text and both made many comments and suggestions that assisted me in putting together the final form of this book. Of the early reviewers of this book, I would particularly like to thank Professor Brad Mundy (Colby College) and Professor Marye Anne Fox (University of Texas, Austin), who made insightful and highly useful suggestions that were important for shaping the focus of the book.

Along the way, many people have helped me with portions or sections of the book. Professor Barry Sharpless (Scripps) reviewed the oxidation chapter and also provided many useful insights into his asymmetric epoxidation procedures. Dr. Peter Wuts (Upjohn) was kind enough to review the protecting group chapter (chapter 7) and helped me focus it in the proper way. Professor Ken Houk (UCLA), Professor Stephen Hanessian (Université de Montréal), Professor Larry Weiler (U. of British Columbia), Professor James Hendrickson (Brandeis), Professor Tomas Hudlicky (U. Florida), and Professor Michael Taschner (U. of Akron) reviewed portions of work that applied to their areas of research and I am grateful for their help.

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Two professors reviewed portions of the final manuscript and not only pointed out errors but made enormously helpful suggestions that were important for completing the book: Professor Fred Ziegler (Yale) and Professor Douglass Taber (U. of Delaware). I thank both of them very much.

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education. These discussions helped shape the way I put the book together.

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I particularly want to thank my wife Sarah and son Steven. They endured the many days and nights of my being in the library and the endless hours on the computer with patience and understanding. My family provided the love, the help, and the fulfillment required for me to keep going and helped me to put this project into its proper perspective. They helped me in ways that are too numerous to mention. I thank them and I dedicate this work to them.

Michael B. Smith

Introducing SpartanModel

SpartanModel is a virtual model kit, designed to provide students of organic chemistry information about molecular structure, stability and properties. In the simplest of terms, *SpartanModel* is the 21st century equivalent of "plastic models" used by students of previous generations. Both provide the means to move from the two-dimensional drawings of molecules to accurate three-dimensional portrayals. However, *SpartanModel* offers a number of significant advantages over plastic models.

The first advantage is that *SpartanModel* overcomes the fact that a plastic model kit contains only a limited number of "parts", perhaps ten or twenty "carbon atoms" and a much smaller number of nitrogen and oxygen atoms. Therefore, only relatively small molecules can be constructed. More importantly, a shortage of parts means that a molecule needs to be disassembled before another molecule can be assembled. This makes it impossible, or in the best circumstances, unnecessarily difficult, to compare the structures of different molecules. *SpartanModel* is unbounded, and molecules with dozens or even hundreds of atoms can be accommodated. Comparisons between different molecules can easily be made.





A related shortcoming of plastic model kits is that they are able to show off just a single aspect of molecular structure, most commonly, the connections (bonds) between atoms. Plastic models that depict overall size and shape are available, but need to be purchased and used separately. On the other hand, models made with *SpartanModel* may be portrayed either to emphasize bonding or to convey information about a molecule's overall size and shape. A further disadvantage is that plastic models "show" but do not "tell" us about important aspects of molecular structure, for example, about the volume that a molecule requires or its surface area. *SpartanModel* provides both a visual image as well as numerical values for these quantities. Of even greater practical value, *SpartanModel* assigns and displays R/S chirality, both for simple molecules where the rules are relatively easy to apply as well as for complex molecules where even an "expert" would be challenged.

Neither *SpartanModel* nor a plastic model kit is able to build proteins. However, *SpartanModel* seamlessly connects to the on-line *Protein Data Bank*¹ (PDB), providing access to >77,000 protein and biomolecule experimental structures. A PDB entry is automatically retrieved given its identifier, and displayed as a "ribbon model" to emphasize the secondary structure. The model may be manipulated enabling detailed visual inspection.



^{1.} H.M. Berman, K. Henrick, H. Nakamura, Nat. Struct. Bio., 10 (12), 980 (2003).

The second advantage is that the structures obtained by *SpartanModel* are not based on the fixed dimensions of the "parts" as they are with plastic models, but rather result from application of quantum mechanics. This means that *SpartanModel* is actually a predictive tool, not merely one following empirical rules. It can be used to explore chemistry.



The third advantage is that the information provided by SpartanModel is not restricted to molecular structure as it is with plastic models. Energies, atomic charges and dipole moments, molecular orbitals and orbital energies as well as electrostatic potential maps may be obtained for any molecule. In addition, heats of formation and infrared spectra for approximately 6000 molecules obtained from high-quality quantum chemical calculations (beyond those provided in SpartanModel) are available from a database included with and accessed from SpartanModel. The availability of energies (as well as selected heats of formation) allows the most stable isomer to be identified and specification of a reaction as endothermic or exothermic. Calculated energies may also be employed to assign the lowestenergy conformation of a molecule and to examine the likelihood that other conformers will be present. The infrared database provides realistic spectra and allows association of individual features in the spectrum with vibrational motions of specific groups of atoms.

In short, while there is utility in the use of plastic model kits, plastic models are severely restricted in terms of the complexity of what can be built, the accuracy of the presentations and in what information they are able to provide.

Some may argue that plastic models are "tried and tested", and that an electronic model kit is unfamiliar or intimidating. We suspect that the vast majority of students will have the opposite perspective. After all, today's students have grown up with computers and expect to use them during their college education. In the final analysis, the choice is not between plastic and computer-based models, but whether or not models have something to offer in a chemist's education. We think that they do.



The easiest way to learn how to use *SpartanModel* is to spend an hour to complete the set of tutorials that are provided with the software. They cover both the use of the program and the interpretation of the quantities that result. Start with **Basic Operations**, which shows how to manipulate molecules, query molecular properties, display molecular orbitals and electrostatic potential maps and draw infrared spectra. Building molecules and performing quantum chemical calculations are not illustrated, but deferred to **Acrylonitrile**. This tutorial should be completed next. The remainder of the tutorials can be completed in any order. **Camphor** and **Androsterone** illustrate construction of successively more complex organic molecules. The first of these provides another example of displaying an infrared spectrum, and both tutorials illustrate the identification and assignment of chiral (R/S) centers. **Acetic Acid Dimer** shows how a molecular complex may be assembled and its binding energy calculated. **1,3-Butadiene** and *trans*-**Cyclooctene** show how energy comparisons among molecules are made. The first involves different conformers of the same molecule and shows how the conformation of a molecule can be changed. The second involves different stereoisomers. **2-Methylpropene** and **Comparing Acid Strengths** illustrate comparisons of molecular orbitals and electrostatic potential maps for different molecules. Finally, **Hemoglobin** shows how to access the Protein Databank (PDB). A part of this tutorial requires that the user be connected to the internet.

PROBLEMS KEYED TO ORGANIC SYNTHESIS

A set of ~60 *problems*, accessible under **Problems** in the **Welcome** screen, has been keyed to the 3rd edition of *Organic Synthesis*. Many of the problems are made up of text (html) files only, opening up a "blank screen" in *SpartanModel*. However, some of the problems include materials that cannot be generated with *SpartanModel* and have been prepared using the full *Spartan* program. These include problems involving transition states and those using LUMO maps and local ionization potential maps. These materials are "read only" and while the models may be examined and manipulated and measurements taken, they may not be altered.

The instructor is free to make additional tutorials and problems using *Spartan*, and to add these to the existing collections. Instructions are provided under *Adding Tutorials and Problems* under the **Help** menu.

TECHNICAL OVERVIEW OF SpartanModel

SpartanModel may be viewed in terms of its components: a molecule builder including a molecular mechanics based scheme for preliminary structure refinement, a real-time quantum chemical engine and two databases.

SpartanModel's builder uses atomic fragments (for example, sp, sp² and sp³ carbon fragments), functional groups (for example, amide and carbonyl groups) and rings (for example, cyclohexane and benzene). Some molecules can be made in just one or two steps ("mouse clicks"), while most others require fewer than ten steps. For example, fewer than 20 steps are required to build the steroid androsterone, the most complicated molecule provided in a tutorial that accompanies *SpartanModel*. Once constructed, molecules can be displayed as to depict bonding (as with most types of plastic models) or overall size and shape (so-called space-filling or CPK models). Associated with the builder is a simple "molecular mechanics" procedure to provide a refined geometry as well as measurement tools for bond distances and angles, volumes, surface areas and polar surface areas (of space-filling models) and for assignment of R/S chirality.

The quantum chemical engine provided in *SpartanModel* may be used to obtain the geometries and properties of the vast majority of molecules encountered in elementary organic chemistry. The desire for open-endedness

(any "reasonable size" molecule may be calculated) together with practical concerns, requires use of a very simple quantum chemical model. The procedure used in *SpartanModel* involves two quantum chemical steps and is preceded by a molecular mechanics² step to ensure a reasonable starting geometry. The first quantum chemical step is calculation of geometry using the PM3³ semi-empirical model and the second step is calculation of the energy and wavefunction at this geometry using the Hartree-Fock 3-21G⁴ model. The resulting wavefunction is used for calculation of the dipole moment and atomic charges and (if requested) graphical displays of the molecular orbitals and electrostatic potential map. PM3 geometry calculations and 3-21G energy calculations for molecules comprising up to 30-40 heavy (non-hydrogen) atoms are likely to require less than one minute on a present day Windows or Macintosh computer.

The quantum chemical calculations in *SpartanModel* properly account for geometry and provide a sound basis for graphical displays of molecular orbitals and electrostatic potential maps. They also provide a qualitatively accurate account of the energies of most types of chemical reactions as well as conformational energy differences. Heats of formation for ~6000 molecules obtained from the T1⁵ thermochemical recipe and included in a database can be used to supplement calculated energies where higher accuracy may be necessary. T1 has been shown to reproduce experimental heats of formation with an rms error of ~8 kJ/mol.

The second database contains infrared spectra for ~ 6000 molecules obtained from the EDF2⁶/ 6-31G* density functional model, adjusted to account for known systematic errors and for finite temperature. The resulting spectra are visually and quantitatively very similar to observed infrared spectra. Vibrational modes associated with individual lines in the spectrum may be "animated".

^{2.} T.A. Halgren, J. Computational Chem., 17, 490 (1996).

^{3.} J.J.P. Stewart, J. Computational Chem., 10, 209 (1989).

J.S. Binkley, J.A. Pople and W.J. Hehre, J. Am. Chem. Soc., 102, 939 (1980); W.J. Pietro, M.M. Francl, W.J. Hehre, D.J. DeFrees, J.A. Pople and J.S. Binkley, *ibid.*, 104, 5039, (1982). For a review and assessment of techniques and computational methods, see: A Guide to Molecular Mechanics and Quantum Chemical Calculations, Wavefunction, Inc., Irvine, CA, USA (2003).

^{5.} W.S. Ohlinger, P.E. Klunzinger, B.J. Deppmeier, W.J. Hehre, J. Phys. Chem. A., 113 10, 2165 (2009).

^{6.} R.D. Adamson, P.M.W. Gill, and J.A. Pople, *Chem. Phys. Lett.*, **284**, 6, (1998).

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Common Abbreviations

E.

Ac	Acetyl	O ン Me
Acac	Acetylacetonate	
AIBN	azo-bis-isobutyronitrile	
All	Allyl	
Am	Amyl	$-CH_2(CH_2)_3CH_3$
aq	Aqueous	
Ax	Axial	
	9-Borabicyclo[3.3.1]nonylboryl	
9-BBN	9-Borabicyclo[3.3.1]nonane	
BINAP	2R,3S-2,2'-bis-(diphenylphosphino)-1,1'-binapthyl	
Bn	Benzyl	-CH ₂ Ph
Boc	<i>t</i> -Butoxycarbonyl	O C Ot-Bu
Bpy (Bipy)	2,2'-Bipyridyl	
Bu	<i>n</i> -Butyl	-CH ₂ CH ₂ CH ₂ CH ₃
Bz	Benzoyl	
CAM	Carboxamidomethyl	
CAN	Ceric ammonium nitrate	$(NH_4)_2Ce(NO_3)_6$
С-	Cyclo-	
cat	Catalytic	
Cbz	Carbobenzyloxy	O CCH ₂ Ph
chap	Chapter(s)	
Chirald	2S,3R-(+)-4-dimethylamino-1,2-diphenyl-3- methylbutan-2-ol	

Other, less common abbreviations are given in the text when the term is used.

CIP	Cahn–Ingold-Prelog	
COD	1,5-Cyclooctadienyl	
СОТ	1,3,5-cyclooctatrienyl	
Ср	Cyclopentadienyl	
CSA	Camphorsulfonic acid	
СТАВ	Cetyltrimethylammonium bromide	$C_{16}H_{33}NMe_{3}^{+}Br^{-}$
Cy (<i>c</i> -C ₆ H ₁₁)	Cyclohexyl	ξ-
°C	Temperature in Degrees Centigrade	
2D	Two-dimensional	
3D	Three-dimensional	
DABCO	1,4-Diazabicyclo[2.2.2]octane	
d	Day(s)	
dba	Dibenzylidene acetone	
DBE	1,2-Dibromoethane	BrCH ₂ CH ₂ Br
DBN	1,5-Diazabicyclo[4.3.0]non-5-ene	
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene	
DCC	1,3-Dicyclohexylcarbodiimide	$c-C_{6}H_{11}-N=C=N-c-C_{6}H_{11}$
DCE	1,2-Dichloroethane	ClCH ₂ CH ₂ Cl
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone	
% de	% Diasteromeric excess	
DEA	Diethylamine	$HN(CH_2CH_3)_2$
DEAD	Diethylazodicarboxylate	EtO ₂ C-N=NCO ₂ Et
DET	Diethyl tartrate	
DHP	Dihydropyran	
DIBAL-H	Diisobutylaluminum hydride	(Me ₂ CHCH ₂) ₂ AlH
Diphos (dppe)	1,2-bis-(Diphenylphosphino)ethane	Ph ₂ PCH ₂ CH ₂ PPh ₂
Diphos-4 (dppb)	1,4-bis-(Diphenylphosphino)butane	Ph ₂ P(CH ₂) ₄ PPh ₂
DIPT	Diisopropyl tartrate	
DMAP	4-Dimethylaminopyridine	
DME	Dimethoxyethane	MeOCH ₂ CH ₂ OMe
DMF	<i>N</i> , <i>N</i> '-Dimethylformamide	
DMS	Dimethyl sulfide	

DMSO	Dimethyl sulfoxide	
dppb	1,4-bis-(Diphenylphosphino)butane	Ph ₂ P(CH ₂) ₄ PPh ₂
dppe	1,2-bis-(Diphenylphosphino)ethane	Ph ₂ PCH ₂ CH ₂ PPh ₂
dppf	bis-(Diphenylphosphino)ferrocene	
dppp	1,3-bis-(Diphenylphosphino)propane	Ph ₂ P(CH ₂) ₃ PPh ₂
dvb	Divinylbenzene	
e-	Electrolysis	
EA	Electron affinity	
% ee	% Enantiomeric excess	
EE	1-Ethoxyethoxy	EtO(Me)CH-
Et	Ethyl	-CH ₂ CH ₃
EDA	Ethylenediamine	H ₂ NCH ₂ CH ₂ NH ₂
EDTA	Ethylenediaminetetraacetic acid	
Equiv	Equivalent(s)	
ESR	Electron Spin Resonance Spectroscopy	
FMN	Flavin mononucleotide	
FMO	Frontier Molecular Orbital	
fod	<i>tris</i> -(6,6,7,7,8,8,8)-Heptafluoro-2,2-dimethyl-3,5-octanedionate	
Fp	Cyclopentadienyl-bis-carbonyl iron	
FVP	Flash Vacuum Pyrolysis	
GC	Gas chromatography	
gl	Glacial	
FVP	Flash Vacuum Pyrolysis	
GC	Gas chromatography	
gl	Glacial	
h	Hour (hours)	
$h_{ m V}$	Irradiation with light	
1,5-HD	1,5-Hexadienyl	
HMPA	Hexamethylphosphoramide	$(Me_2N)_3P=O$
HMPT	Hexamethylphosphorus triamide	$(Me_2N)_3P$
¹ H NMR	Proton Nuclear Magnetic Resonance Spectroscopy	
НОМО	Highest occupied molecular orbital	
HPLC	High performance liquid chromatography	
HSAB	Hard/Soft Acid/Base	

IP	Ionization potential	
<i>i</i> -Pr	Isopropyl	-CH(Me) ₂
IR	Infrared spectroscopy	
LICA (LIPCA)	Lithium cyclohexylisopropylamide	
LDA	Lithium diisopropylamide	LiN(<i>i</i> -Pr) ₂
LHMDS	Lithium hexamethyl disilazide	LiN(SiMe ₃) ₂
LTMP	Lithium 2,2,6,6-tetramethylpiperidide	
LUMO	Lowest unoccupied molecular orbital	
МСРВА	meta-Chloroperoxybenzoic acid	
Me	Methyl	-CH ₃ or Me
MEM	β–Methoxyethoxymethyl	MeOCH ₂ CH ₂ OCH ₂ -
Mes	Mesityl	2,4,6-tri-Me-C ₆ H ₂
min	minutes	
MOM	Methoxymethyl	MeOCH ₂ -
Ms	Methanesulfonyl	MeSO ₂ -
MS	Molecular Sieves (3Å or 4Å)	
MTM	Methylthiomethyl	
MVK	Methyl vinyl ketone	MeSCH ₂ -
NAD	Nicotinamide adenine dinucleotide	
NADP	Sodium triphosphopyridine nucleotide	
Napth	Napthyl (C ₁₀ H ₈)	
NBD	Norbornadiene	
NBS	N-Bromosuccinimide	
NCS	N-Chlorosuccinimide	
NIS	<i>N</i> -Iodosuccinimide	
Ni(R)	Raney nickel	
NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide	
Nu (Nuc)	Nucleophile	
OBs	O-Benzenesulfonate	
Oxone	$2 \text{ KHSO}_5 \bullet \text{KHSO}_4 \bullet \text{K}_2 \text{SO}_4$	
P or	Polymeric backbone	
PCC	Pyridinium chlorochromate	
PDC	Pyridinium dichromate	
PEG	Polyethylene glycol	

Ph	Phenyl	٤-
PhH	Benzene	
PhMe	Toluene	
Phth	Phthaloyl	
Pip	Piperidino	·Ś·N
PPA	Polyphosphoric acid	
PPTS	<i>para</i> -Toluenesulfonic acid	
Pr	<i>n</i> -Propyl	-CH ₂ CH ₂ CH ₃
Ру	Pyridine	N
Quant	Quantitative yield	
Red-Al	[(MeOCH ₂ CH ₂ O) ₂ AlH ₂]Na	
RT	Room temperature	
sBu	sec-Butyl	CH ₃ CH ₂ CH(CH ₃)
sBuLi	sec-Butyllithium	CH ₃ CH ₂ CH(Li)CH ₃
S	seconds	
sec	sections(s)	
SEM	2-(trimethylsilyl)ethoxymethyl	
SET	Single electron transfer	
Siamyl	sec-Isoamyl	(CH ₃) ₂ CHCH(CH ₃)-
(Sia) ₂ BH	Disiamylborane	
TASF	<i>tris-</i> (Diethylamino)sulfonium difluorotrimethyl silicate	
TBAF	Tetrabutylammonium fluoride	$n-\mathrm{Bu}_4\mathrm{N}^+\mathrm{F}^-$
TBDMS	<i>t</i> -Butyldimethylsilyl	t-BuMe ₂ Si
TBHP (<i>t</i> -BuOOH)	t-Butylhydroperoxide	Me ₃ COOH
<i>t</i> -Bu	<i>tert</i> -Butyl	-CMe ₃
TEBA	Triethylbenzylammonium	$Bn(Et_3)_3N^+$
TEMPO	Tetramethylpiperidinyloxy free radical	
TFA	Trifluoroacetic acid	CF ₃ COOH
TFAA	Trifluoroacetic anhydride	$(CF_3CO)_2O$
Tf (OTf)	Triflate	$-SO_2CF_3$ ($-OSO_2CF_3$)

ThexBH ₂	Thexylborane (<i>tert</i> -hexylborane)	
THF	Tetrahydrofuran	
THP	Tetrahydropyran	
TMEDA	Tetramethylethylenediamine	Me ₂ NCH ₂ CH ₂ NMe ₂
TMS	Trimethylsilyl	-Si(CH ₃) ₃
TMP	2,2,6,6-Tetramethylpiperidine	
Tol	Tolyl	$4-(Me)C_6H_4$
TPAP	Tetrapropylperruthenate	
Tr	Trityl	-CPh ₃
TRIS	Triisopropylphenylsulfonyl	
Ts(Tos)	Tosyl = <i>p</i> -Toluenesulfonyl	$4-(Me)C_6H_4SO_2$
UV	Ultraviolet spectroscopy	
X _c	Chiral auxiliary	

chapter Retrosynthesis, Stereochemistry, and Conformations

1.1. INTRODUCTION

Where does one begin a book that will introduce and discuss hundreds of chemical reactions? To synthesize a complex organic molecule many reactions must be used, and the strategy used for that synthesis must consider not only the type of reaction but also the mechanism of that reaction. We begin with a brief introduction to synthetic planning. A full discussion of strategies for total synthesis will be introduced in chapter 10, but surveying the fundamental approach can help one understand how reactions are categorized.

The total synthesis of complex natural products usually demands a thorough knowledge of reactions that form carbon-carbon bonds as well as those that change one functional group into another. Examination of many syntheses of both large and small molecules, reveals that building up a carbon skeleton by carbon-carbon bond forming reactions is rarely done successfully unless all aspects of chemical reactivity, functional group interactions, conformations, and stereochemistry are well understood. The largest number of actual chemical reactions that appear in a synthesis do not make carbon-carbon bonds but rather manipulate functional groups.



Changing one functional group into another is defined as a **functional group interchange** (FGI). Simple examples are the loss of H and Br from 2-bromo-2-methylpentane (1) to form 2-methyl-2-pentene (2), or oxidizing the alcohol unit in 2-pentanol (3) to the carbonyl unit in 2-pentanone (4). Contrast these reactions with a reaction that brings reactive fragments together to form a new bond between two carbon atoms, such as the condensation of two molecules of butanal (5) under basic conditions to give 6, which is known as the **aldol condensation**. The aldol condensation forms a carbon-carbon bond but before such a reaction can occur one usually must incorporate or change key functional groups. This observation is an important reason that more functional group exchange reactions are typically required, relative to carbon-carbon bond forming reactions. Several different functional groups may also be structural units of the molecule being synthesized.

Nowadays, the relationship of two molecules in a synthesis is commonly shown using a device known as a **transform**, defined by Corey and co-workers¹ as: "the exact reverse of a synthetic reaction to a target structure". The **target structure** is the final molecule one is attempting to prepare. The synthetic transformation that converts butanal (5) to hydroxy-aldehyde **6** via the **aldol condensation** (see sec. 9.4.A) is an example. The transform for this synthetic step is, therefore, $\mathbf{6} \Rightarrow \mathbf{5}$. Inspection of **6** and **5** reveals that mentally breaking the highlighted bond (bond *a*) in **6** (represented by the squiggly line) leads to disconnect fragments **5** and **7** and in this process bond *a* is said to be **disconnected**. An elementary disconnection approach quickly becomes an integral part of how one thinks about molecules. The focus here, however, is on how to put molecules together. How does the disconnection approach assist us in this endeavor? Understanding why bond *a* is important comes from a thorough knowledge of the chemical properties of compound **6**. When we disconnect bond *a*, we eventually want to make that bond by a chemical reaction. To understand the molecular characteristics of **6** that led us to disconnect bond *a*, we must understand the chemical reactions required to form that bond.



Pentanoic acid (8) is a simple target that illustrates the approach. Disconnection of the carbon-carbon bond marked a leads to 1-butanol (9) as the precursor (the starting material). Analysis of the



targeted carboxylic acid as well as the product alcohol shows a change in oxidation state, and a one-carbon extension of the carbon chain. Of the four carbon-carbon bonds in target **8**, bond *a* must be used to attach the carbonyl to the starting material **9**. Disconnection of bond *a* leads to the simplified structure **10** and the CO₂H (carboxyl) fragment, which is not a real molecule. These two structures are termed **disconnect products** but **10** contains an unspecified X group, that must be a reactive functional group and could be hydroxyl (as in **9**). In addition, the carboxyl fragment shown does not exist and a **synthetic equivalent** of the disconnect product that is a real molecule must be found. In other words, to complete any reaction a real molecule or reagent must be used who reaction generates the disconnect fragment directly. Alternatively, a surrogate can be used to give a product that can be converted to the fragment. For example, in the disconnection C–NH₂ to C and NH₂, ammonia reacts with an alkyl halide to give an amine, but there are problems with over-alkylation. The NH₃ is the direct equivalent

^{1.} Corey, E.J.; Cheng, X. The Logic of Chemical Synthesis, Wiley-Interscience, NY, 1989.

of NH₂. To overcome such problems, the phthalimide anion reacts with an alkyl halide to give the phthalimide, and subsequent reaction with hydrazine liberates the amine. Phthalimide is a surrogate for NH₂, used to circumvent problems with the ammonia reaction. In the case of **8**, we require a COOH surrogate, since COOH is not a real molecule. It is known that carbon dioxide (CO₂) reacts with Grignard reagents (**10**, where X = MgBr) to give a carboxylic acid after hydrolysis of the resulting carboxylate salt in a second step. Therefore, the disconnection shown is a viable process since we know a chemical reaction to make that bond. Working backward in this manner is termed **retrosynthetic analysis** or **retrosynthesis**, defined by Corey as "a problem-solving technique for transforming the structure of a synthetic target molecule to a sequence of progressively simple materials along a pathway which ultimately leads to a simple or commercially available starting material for chemical synthesis".²



Based on our retrosynthetic analysis, one solution to this synthetic problem is to use the reaction of cyanide ion with primary halides via second order nucleophilic substitution ($S_N 2$, see sec. 2.6.A), to generate a nitrile. The cyano unit is readily hydrolyzed to an acid. Is there an alternative? The answer is yes via a Grignard reaction with carbon dioxide (sec. 8.4.C.iv), but this strategy requires that alcohol **9** be converted to an alkyl halide and then to the corresponding Grignard reagent. Subsequent reaction with carbon dioxide and hydrolysis will give **8**. Formation of an alkyl halide from an alcohol is a functional group interchange (FGI) reaction (see sec. 2.8.A), as is conversion of the halide to a nitrile and the nitrile to an acid. The retrosynthesis effectively describes the reactions necessary for the real synthesis starting from **8**, but reagents must be added to complete the synthesis. Determining the key bond for disconnection in the target led to the conclusion that the synthesis required a carbon-carbon bond forming reaction as well as FGI reactions. Thinking about the synthesis and disconnections led us to analyze and understand the reactions that must be used.

It is important to point out that rarely does one take a retrosynthetic analysis and use the exact reverse track with simple reagents to synthesize the target. For mono-functional molecules this approach often works, but for molecules with multiple functionality, particularly complex natural products, the idea of doing a retrosynthetic analysis and simply providing reagents to convert the starting material to the target is very naïve. There are usually steps that simply do not work using available reagents or those suggested by literature precedent, and the reactions may give poor yields or the wrong stereochemistry. There are unanticipated interactions of functional groups and unexpected requirements for protecting groups. In short, the approach shown here is a beginning, intended to get you to think about how to pull molecules apart, what reactions may be appropriate to put them together again, and to think about strategies

^{2.} Reference 1, p 6.

for synthesis. These ideas are elaborated in chapter 10. When we ask how 8 is prepared from 9, we are forced to examine how many reactions that form carbon-carbon bonds we actually know how to use, as well as those reactions that prepare and interchange functional groups. In other words, it forces us to review our understanding of Organic chemistry. Other important concepts in Organic chemistry must be brought to bear, including stereochemistry and conformational theory.



The importance of stereochemistry is illustrated by the disconnection sequence $11 \Rightarrow 12 \Rightarrow 13 \Rightarrow 14$, described by Corey.³ The second transform involves a **Dieckmann condensation** reaction (see sec. 9.4.B.ii), and several steps are required to prepare 13 from 14. Focus attention on the stereochemical relationship of the various groups and of the ring juncture. It is insufficient to consider methods that simply make a bond, because we must be able to form the bond with control of the relative and absolute stereochemistry.



Another important analysis of organic reactions can be found in the transform $15 \Rightarrow 16A$. Why does this transform lead to the relative stereochemistry (trans) shown in 15? The proper spatial relationship of the functional groups in the target must be known prior to making the choice for a chemical reaction. This relationship can be difficult to see using the two-dimensional (2D) structures shown. A different model of the molecule such as a 3D-model will usually

^{3.} Reference 1, p 13.

give a better understanding of stereochemical and conformational relationships. In this case, representation **16B** (produced by the computer program Spartan 06^{TM})⁴ provides much more detail than **16A**, and shows that the hydroxyl group is positioned on one side of the carbonyl. If a chelating metal such as zinc is used with the reducing step (zinc borohydride, see sec. 4.4.B), coordination with the hydroxyl (**17**) may deliver hydride primarily from the same face as the CH₂OH unit, leading to the observed trans stereochemistry in **18**. In this example, the **conformation** (3D shape) of the molecule provides a model that helps us understand the stereochemical outcome of the reaction.

Three important factors will be reviewed in this chapter: (1) disconnection and retrosynthesis, (2) stereochemistry, (3) conformational analysis. This review will not to formally introduce synthesis (synthetic theory will be presented in chapter 10),⁵ but focus attention on concepts that help us understand reactions.

1.2. THE DISCONNECTION PROTOCOL

When retrosynthetic theory is introduced, it is easy to become embroiled in making the "correct" disconnection rather than focusing on the chemical reactions and concepts required to form the disconnected bond in the synthesis. In reality, the disconnection is dictated by the ability to form the bond in the context of stereochemistry and selectivity, not the other way around. The synthesis of organic molecules dates to the nineteenth century, but the work of Perkin, Robinson and others in the early twentieth century demonstrated the importance of synthetic planning.¹ In the 1940s and 1950s, Woodward, Robinson, Eschenmoser, Stork and others clearly showed how molecules could be synthesized in a logical and elegant manner. In the 1960s, Corey identified the rationale behind his syntheses, and such logical synthetic plans (termed retrosynthetic analyses) are now a common feature of the synthetic literature.² The disconnection approach is used to teach synthesis, and Warren has several books that describe this approach in great detail.⁶ Several different strategies for the synthesis of organic molecules are available (see chapter 10) and all are useful. When these strategies are applied to a first synthesis in an introductory course, the most critical issue raised after a disconnection is what to do with the disconnect products. All disconnection approaches assign priorities to bonds in a molecule and disconnect those bonds with the highest priorities, as with Corey's

^{4.} Spartan[™] is a trademark of Wavefunction Inc., Irvine, CA, Spartan'06.

 ⁽a) Corey, E.J.; Wipke, W.T. Science, 1969, 166, 178; (b) Corey, E.J.; Long, A.K.; Rubinstein, S.D. Ibid 1985, 228, 408; (c) Corey, E.J.; Howe, W.J.; Pensak, D.A. J. Am. Chem. Soc. 1974, 96, 7724; (d) Corey, E.J. Quart. Rev. Chem. Soc. 1971, 25, 455; (e) Corey, E.J.; Wipke, W.T.; Cramer III, R.D.; Howe, W.J. J. Am. Chem. Soc. 1972, 94, 421; (f) Corey, E.J.; Jorgensen, W.L. Ibid 1976, 98, 189.

 ⁽a) Warren, S. Organic Synthesis: The Disconnection Approach, John Wiley, Chichester 1982; (b) Warren S. Workbook for Organic Synthesis: The Disconnection Approach, John Wiley, Chichester 1982; (c) Warren, S. Designing Organic Synthesis: A Programmed Introduction to the Synthon Approach, Wiley, Chichester 1978. Also see (d) Wyatt, P.; Warren, S. Organic Synthesis, Strategy and Control, Wiley, New Jersey, 2007.

strategic bond analysis (see sec. 10.5).^{1,5} Smith described a simple method where the priorities are based only on the relative ability to chemically form the bond broken in the disconnection,⁷ based on known reactions.



In a typical introductory Organic chemistry course, there are two fundamental types of synthesis problems. In the first, both the starting material and the target are specified. In the second, only the final target is given and the synthetic chemist must deduce the starting material. This latter case usually poses a more difficult problem. We can illustrate the fundamentals of a retrosynthetic analysis with the first type of problem, and will delay discussion of the second type until Chapter 10. In the disconnection $19 \Rightarrow 20$, 2-butene is the designated starting material, which means that the target (19) is to be synthesized from 2-methylpropene (20). The four carbons of 20 must be "located" in 19 since this will define the carbon atoms that must be disconnected for the synthesis. The presence of two methyl groups in 20 limits the possibilities, and there are two different locations where the four carbons in isobutene may be found (see **19B** and **19C**). If we choose the pattern shown in **19B**, this dictates that bond a must be disconnected. If we choose the pattern in **19C**, then bond b must be disconnected. Disconnection of bond a in 19B leads to two fragments (disconnect products), 21 and 22. Similarly, disconnection of bond b in 19C leads to disconnect products 23 and 24. Both disconnections must be considered, but structures 21-24 are not real molecules so we cannot evaluate the relative merit of each disconnection using these fragments. Real molecules and real reactions are required. Therefore, two assumptions will be made: (1) The key carboncarbon bonds will be formed by a small subset of reactions and (2) the bonds will be made by reactions involving polarized or ionic intermediates.



The first assumption is based on the carbon-carbon bond-forming reactions shown in Table 1.1,⁷ which are usually presented in a typical sophomore Organic chemistry course. The second

^{7.} Smith, M.B. J. Chem. Educ. 1990, 67, 848.

assumption is based on the observation that all reactions in the table except entry 10 (the **Diels-Alder reaction**, see sec. 11.4.A) involve highly polarized or ionic intermediates. With this assumption in hand, it is reasonable to assume that the disconnections generated from **19** will lead to ionic or polarized intermediates, and we can form the carbon-carbon bonds with one of the reactions found in Table 1.1. These assumptions allow us to convert each disconnect product (**21-24**) into a polarized fragment.



Table 1.1. Carbon-Carbon Bond-Forming Reactions

The concept of nucleophilic and electrophilic atoms in ionic and polarized intermediates is well known. Polarized bond notation such as $C^{\delta+}$ -Br^{$\delta-$} and $C^{\delta-}$ -Li^{$\delta+$} is commonly used in describing the reactivity of such bonds. The polarizability of various atoms and molecules is also reflected in hard and soft acid and base (HSAB) theory (see sec. 2.4).⁸ Seebach used structure **25** to formalize a bond polarization model.⁹ The sites marked *d* in **25** represent *donor* sites or *nucleophilic* atoms. The sites marked *a* are *acceptor* sites and correspond to

^{8.} Ho, T-L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*, Academic Press, New York, **1971**, pp 1-3 and 27-34.

^{9.} Seebach, D. Angew. Chem. Int. Ed. 1979, 18, 239.

electrophilic atoms. Bond polarization induced by the heteroatom extends down the carbon chain, due to the usual inductive effects that are a combination of through-space and through-bond effects.¹⁰ The electrophilic carbon adjacent to X (C1 for example) is designated C^a (an acceptor atom) since proximity to the δ - electronegative atom (X) induces the opposite polarity. Similarly, C2 is a donor atom (C^d), but less polarized than X (this carbon is further away from the electrons that induce the bond polarization), and C3 is a weak acceptor atom. As a practical matter, the effect is negligible beyond C4 and will be ignored.

If this protocol is applied to disconnect fragments $21 \rightarrow 24$, either carbon at the point of disconnection can be assigned as a donor (d) or an acceptor (a) giving four different possibilities. Disconnect products 21 and 22, for example, become 26 or 27 and 28 or 29, respectively. Fragments $26 \rightarrow 29$ are not real molecules, and another step is required before the best donoracceptor pair can be chosen. Each fragment must be correlated with a synthetic equivalent. Table 1.2^7 provides a list of common synthetic equivalents, leading to the definition of **synthetic** equivalent as a molecular fragment that is equivalent to a real molecule by virtue of its chemical reactivity.¹¹ A C^d site on an unfunctionalized carbon, for example, is equivalent to the C^{δ -} of a Grignard reagent (see sec. 8.4) and a C^a site on an unfunctionalized carbon is equivalent to the electrophilic carbon on an alkyl halide. Each synthetic equivalent in Table 1.2 is based on an ionic or highly polarized nucleophilic substitution or nucleophilic acyl addition reaction. Using Table 1.2, fragment 26 is the equivalent of a Grignard reagent, 30 (an organocuprate such as [Me₂CHCH₂]₂CuLi can also be used as in sec. 8.7.A). The equivalent of its partner (fragment 27) is α -chloroketone 31. Similarly, the synthetic equivalent of 28 is bromide, 32 (another halide can be used) and the equivalent of 29 is an enolate anion, 33 (see sec. 9.2, 9.3). In the actual synthesis, 30 will react with 31 and 32 will react with 33, and both reactions will produce 19. Bromide 32 is derived from the 2-methylpropene starting material, but the functional group must be modified. To accomplish this, the chemical relationship between the C-C-Br and C=C must be known. In other words, what reagents are required to transform an alkyl a halide into an alkene, and vice-versa. Figure 1.1⁷ provides a functional group reaction diagram to interconvert one functional group into another by known chemical pathways. Since



 ⁽a) Baker, F.W.; Parish, R.C.; Stock, L.M. J. Am. Chem. Soc. 1967, 89, 5677; (b) Golden, R.; Stock, L.M. Ibid 1966, 88, 5928; (c) Holtz, H.D.; Stock, L.M. Ibid 1964, 86, 5188; (d) Branch, G.E.K.; Calvin, M. The Theory of Organic Chemistry, Prentice-Hall: New York, 1941, chapter 6; (e) Ehrenson, S. Progr. Phys. Org. Chem. 1964, 2, 195; (f) Roberts, J.D.; Carboni, C.A. J. Am. Chem. Soc. 1955, 77, 5554; (g) Clark, J.; Perrin, D.D. Quart. Rev. Chem. Soc. 1964, 18, 295.

^{11.} See Reference 1, p 30.
Table 1.2. Common Synthetic Equivalents for Disconnect Products

an alkene and a halide are chemically related by the reactions indicated, either could be used in the disconnect product since one can easily be converted to the other at the appropriate time. Similar analysis of disconnect fragments 23 and 24 may lead to different reactive fragments, giving a different synthesis.



Figure. 1.1. Functional Group Exchange Reaction Wheel. A Visual Reminder of the Interconvertibility of Functional Groups.

In most undergraduate Organic chemistry textbooks, the functional group approach to introducing chemistry means that groups with related chemical properties may be presented in different semesters. Although alkenes and carbonyl both react as a base in the presence of an acid, these groups are presented at different places and at different times during a typical course. The approach can make the relationship of one functional group to another difficult to see. Figure 1.1⁷ provides a visual reminder of these relationships, which are often essential for completion of a total synthesis. In the context of this chapter, it illustrates chemical relationships that can be used to understand functional group interchange reactions. In the example at hand, the relationship between a bromide and an alkene is apparent from the table (C-C-Br \Rightarrow C=C). It is also possible to write a functional group exchange based on the alkene as C=C \Rightarrow C-C-Br.

It is important to emphasize that Figure 1.1 is *not* intended as a device to memorize specific reactions, but rather to introduce the idea of using various functional groups in a synthesis by recognizing their synthetic relationships. Synthetic sequences for *both* disconnections *a* and *b* are shown. The best route is probably involves conversion of **20** to 1-bromomethyl-propane and reaction with enolate **33** (see sec. 9.2, 9.3.A), which is derived from 3-methyl-2-butanone. This synthesis is considered to be better than the second one shown (based on disconnection *b*) since it involves simpler reagents and is shorter (fewer chemical steps). The synthetic chemist must decide which is best, however, based upon his or her own experience and goals. The best route is a subjective judgment, although it usually makes more sense to follow a short and simple route rather than a long and complex one.



1.3. BOND PROXIMITY AND IMPLICATIONS FOR CHEMICAL REACTIONS

How is the synthetic analysis just presented related to a study of chemical reactions? In all of these disconnections, we converted the disconnect products to actual compounds so we could predict which chemical reactions might work. In all cases, the disconnected bonds were either the one directly attached to the functional group (C-X) or the one next to it (C-C-X). We can use these observations to understand what reaction types are important for making C-C bonds.

When a functional group (X) is attached to a carbon atom, the bond polarity is important to about the third bond, as indicated in **25**. If we make the *assumption* that most reactions involve highly polarized species, then the three bonds just mentioned become very important. The three important bonds are the C-X bond (called the α bond), the adjacent one (the β bond), and the γ bond, as seen in **34**. If we disconnect the α bond, the synthetic step to form that bond requires direct attack of an X group (where X is an heteroatom) on a suitably functionalized carbon. This process is illustrated by **35**, where a nucleophilic X group attacks the electrophilic

carbon. A simple example is the reaction of azide ion (N_3^-) with 1-iodopropane to give 1azidopropane. If we disconnect the β bond, we obtain **36**, where the natural bond polarization suggests a reaction in which a nucleophilic carbon species attacks the electropositive carbon of the C-X unit. If we assume the functional group is C=O, addition of a Grignard reagent to an aldehyde fits this description. Finally, disconnection of bond γ leads to **37** (also see Chapter 10), and conjugate addition of an organocuprate to a α , β -unsaturated ketone fits this type of disconnection (where X is C=O).

The point of this section is to show how disconnection of molecules that contain polarized functional groups c an be based on natural bond polarization characteristics. This analysis is based on a variety of common reactions, which is important not only for planning a synthesis but for understanding how chemical reactions work. This general theme will be elaborated in many chapters to follow.



1.4. STEREOCHEMISTRY



The concept of chirality and absolute configuration is introduced early in undergraduate Organic chemistry courses. For that reason, this section is intended as a review and it is assumed the reader has some familiarity with the concepts.

This section will discuss stereoisomers, particularly enantiomers and diastereomers. We will begin with chlorides **38** and **39**, which have the same empirical formula but are clearly different molecules. They are isomers: two or more molecules that have the same empirical formula. They are different molecules! The term isomer does not adequately characterize the relationship between **38** and **39**, since they are of the same chemical type. The term used to define the relationship between **39** and **38** is **regioisomer**: two or more molecules with the same empirical formula, but with a different attachment of the atoms (*different connectivity*).

Another type of isomerism occurs when two molecules have the same empirical formula and also have the same conductivity of atoms but are different molecules. They differ only in the

relative spatial positions of the atoms, and are called **stereoisomers**.¹² The following sections will discuss different types of stereoisomers and their characteristic properties.

1.4.A. Absolute Configuration in Chiral Nonracemic Molecules

When an atom is bound to four different atoms or groups in a tetrahedral arrangement, that atom is said to be **stereogenic** or chiral. The second carbon (C^*) in 2-chlorobutane (**38**) is a stereogenic center. The C* in **39** is not stereogenic, since that carbon has two identical atoms (H) attached to it. Why is identification of C* in **38** as a stereogenic center important? The answer appears when the mirror image of **38** is drawn (see **40**), and the Cl of **38** is reflected into the Cl in **40**. In addition, hydrogen reflects to hydrogen, methyl to methyl, and ethyl to ethyl, but



this process leads to two different molecules. 2-Chlorobutanes **38** and **40** are *not superimposable* by any rotation of bonds, or positioning of the molecules, and they are *different molecules*. More precisely, the molecules have no symmetry (they are asymmetric)¹³ as can be seen in **41**, which is an attempt to superimpose **38** and **40**. It is clear that while the Me and Et groups superimpose in **41**, the Cl and H atoms do not. Confirm this for yourself with any manual or electronic model, by making both enantiomers and trying to make all groups superimpose. They do not! 2-Chlorobutanes **38** and **40** are different molecules, but they are clearly isomers, and they are closely related since they are mirror images. They are not regioisomers because the connectivity of atoms is the same. These two molecules are **stereoisomers** (molecules that differ in their spatial arrangement of atoms but have the same point of attachment).¹² 2-Chlorobutanes **38** and **40** are further distinguished as a special type of stereoisomer called **enantiomers**, that is, stereoisomers that are nonsuperimposable mirror images. If a structure

^{12.} For a general discussion of stereoisomers, see Eliel, E.L.; Wilen, S.H.; Mander, L.N. Stereochemistry of OrganicCompounds, Wiley-Interscience, New York, **1994**, pp 49-70.

^{13.} For a general discussion of symmetry, symmetry operators and their importance in organic chemistry, see Ref. 12, pp 71-99.

and its mirror image are superimposable by rotation or any motion other than bond making and breaking, then they are identical (a single molecule and not enantiomers; **39** is an example). Make a model of **39** and its mirror image and demonstrate that they are superimposable. When molecules contain more than one stereogenic center, diastereomers (a new type of stereoisomer) will be present, but this will be discussed in sec. 1.4.B.



Figure 1.2. The Steering-Wheel Model. In Part, Rreprinted with permission from Cahn, R.S. and the Journal of Chemical Education, Vol. 41, **1964**, 116-125. Copyright 1964, Divison of Chemical Education, Inc.

Since 2-chlorobutanes **38** and **40** are different molecules, each must have a unique identifier that allows one enantiomer to be distinguished from the other. The method used is the (R/S) system, which employs a set of priority rules developed by Cahn, Ingold, and Prelog.¹⁴ In this system, each atom attached to the stereogenic center is assigned a priority (a to d, where a is the highest priority atom and d is the lowest priority atom). Using the **steering wheel model** (see Figure 1.2) the viewer positions the molecule in such a way that one can sight down the C*-Z^d bond, with Z^d projected away from the viewer, as shown. An imaginary line $a \rightarrow b \rightarrow c$ is drawn and inspected to see if that line of rotation around the wheel follows a clockwise (right) or a counterclockwise (left) path. If the $a \rightarrow b \rightarrow c$ sequence is clockwise the enantiomer is assigned the (R) configuration. Conversely, if it is counterclockwise, the enantiomer is assigned the (S) configuration. When applying this model, the molecule *must* be rotated so that d is Z^d prior to sighting down the C*-Z^d bond. Several different molecular representations are shown below, along with the correct orientation for determining the (R/S) configuration.

 ⁽a) Prelog, V.; Helmchen, G. Angew. Chem. Int. Ed. 1982, 21, 567; (b) Cahn, R.S. J. Chem. Educ. 1964, 41, 116 (see p 508); (c) Cahn, R.S.; Ingold, C.; Prelog, V. Angew. Chem. Int. Ed. 1966, 5, 385; (d) Cahn, R.S.; Ingold, C.K. J. Chem. Soc. (London) 1951, 612; (e) Cahn, R.S.; Ingold, C.K.; Prelog, V. Experientia 1956, 12, 81.



Determining the relative priority (*a* to *d*) is accomplished by a series of rules just mentioned, the so-called **Cahn-Ingold-Prelog (or CIP) selection rules**.^{14,15,16}

- 1. Atoms with a higher atomic number precede atoms of lower atomic number
 - $O \hspace{0.2cm} > \hspace{0.2cm} N \hspace{0.2cm} > \hspace{0.2cm} C \hspace{0.2cm} > \hspace{0.2cm} H$

2. Isotopes with a higher mass number precede isotopes of lower mass number

This rule applies to isotopes such as tritium, deuterium and protium $({}^{3}\text{H} > {}^{2}\text{H} > {}^{1}\text{H})$. These two rules are illustrated first by 1-bromo-1-chloroethane (42), where Br > Cl > Me > H and the $a \rightarrow b \rightarrow c$ rotation is clockwise, giving an (*R*) configuration. Similarly, in 1-deuterioethanol (43) the priority is O > C > D > H and the $a \rightarrow b \rightarrow c$ sequence is also clockwise for an (*R*) configuration. Note the use of a Fischer projection for 43, where the horizontal lines project out of the paper towards you, and the vertical line projects behind the paper. Fischer projections are not used as much nowadays.



A problem arises when two of the atoms (not the groups) attached to C* are the same. In 4-methylhex-5-en-1,3-diol (44), the priorities of the atoms attached to C* are O > C \approx C > H. Rules 1 and 2 do not allow us to distinguish the two carbon atoms. A new rule is required to solve this problem.



^{15.} Reference 12, pp 101-112.

^{16.} IUPAC Commission on Nomenclature of Organic Chemistry Pure Appl. Chem. 1974, 45, 13.

3. When the highest priority atoms are identical, compare the number of priority atoms at the first point of difference to distinguish them.

Generic priorities by this rule are:

$$C^{CCC} > C^{CCH} > C^{CHH} > C^{HHH}$$

and
 $C^{OOO} > C^{OOC} > C^{OCC} > C^{CCC}$

Examination of **44** reveals that the two carbon atoms attached to C* are C^{CHH} and C^{CCH}. The secondary carbon has a higher priority than the primary carbon. The absolute configuration of **44** is (*S*). Another example is the ketal, **45**. The priority analysis is $[C^*-O-C^{CHH} = b]$, $[C^*-O-C^{CCH} = a]$ and $[C^*-C^{CHH}-C^{HHH} = d]$, $[C^*-C^{CHH}-C^{CHH} = c]$ so the absolute configuration of **45** is (*R*).



There is another problem in example **45**. As one proceeds down the carbon chain, the ethyl (C^{CHH}) and butyl (C^{CHH}) groups have the same atoms attached directly to C*, and are therefore considered to have identical priorities (no point of difference). To determine the priority, follow the chain to the next carbon of the ethyl and the butyl where there is a point of difference (C^{HHH} versus C^{CHH}). Similarly, the oxygen chains show no point of difference with oxygen attached to C* in both cases (O^{CHH}), but a point of difference was reached at the carbon attached to each oxygen atoms ($O-C^{CHH}$ versus $O-C^{CCH}$), and this analysis can be formalized as a general rule.

4. When the first point of difference contains two or more identical atoms, proceed atom by atom down the highest priority chain to the next point of difference and apply rules 1, 2 or 3 to determine the priority.

One must proceed down a chain to find a point of difference in 3-hydroxy-1-aminohexane (46), which shows the following priority for atoms attached to C*: O (a) > C ~ C > H (d). Comparing the two chains gives [C*-C^{CHH}-C^{NHH} = b] and [C*-C^{CHH}-CH^{CHH} = c].



It is necessary to go to the second atom to find a point of difference that will distinguish these groups, and **46** has an (S) configuration. Similarly, 1-bromo-7-methyl-7-tetradecanol (**47**) shows the hydroxyl O and the methyl group to be (a) and (d), respectively, but to determine (b) and (c) requires analysis to the sixth carbon in each chain. This priority establishes the (S) configuration.



In **48**, the methyl and hydrogen are assigned the priorities (*c*) and (*d*). To determine the *a* and *b* priorities we must focus on the two arms that contain OCH. The highest priority chain is along C-O-C (the oxygen chain), but both groups are $O^{C}-C^{HHH}$. They are identical and we cannot use them to establish the priority. In such a case, the lower priority carbon chain must be used (in this case, the isopropyl and ethyl groups rather than the methoxy groups), giving C*-C^{OCH}-C^{CCH} for (*a*) and C*-C^{OCH}-C^{CCH} for (*b*) and the molecule has the (*S*) configuration.



A common misconception for rules 3 and 4 arises from an incorrect interpretation of rules 1 and 2. In **49**, methyl and hydrogen are the (*c*) and (*d*) groups. An analysis by rule 3 predicts $C^{CCH} > C^{CHH}$. In the C^{CHH} chain (-CH₂CH₂CH₂OH), however, there is an oxygen. The CH(Me)CH₂CH₂CH₂CH₃ (C^{CCH}) chain does not contain a heteroatom. *The rules dictate that the priority be determined at the first point of difference, not the second*. The presence of the oxygen is, therefore, irrelevant and the C^{CCH} chain will



have priority over the C^{CHH} chain. The absolute configuration of **49** is (*S*). Cyclic compounds are treated by the same rules, but each arm of the ring is viewed as a different group and then compared atom-by-atom. 3-Chlorocycloheptanone (**50**), for example, has $Cl(a) > C \approx C > H(d)$. The carbonyl chain is C*-C^{CHH}-C^{OO°C} (*b*), in contrast with the carbon arm, C*-C^{CHH}-C^{CHH} (*c*). The configuration is (*R*).



In **51**, the methyl and hydrogen are again (*c*) and (*d*), but the rings pose a problem, one arm of the ring points to chlorine and one to hydroxyl. Since the secondary hydroxy carbon is closest to C^* , the bottom arm of each ring is followed rather than the top arm. By this route, the left ring is highest priority:

 $(C^*-C^{CCH}-C^{COH}-C^{CCH}-C^{CCH}-C^{CCH}-C^{CCH}-C^{CCH}-C^{CCH})$, and the absolute configuration is (*S*).



Cycloheptanone (**50**) contained a carbonyl, and the analysis treated that carbon as C^{OOC} . Where did the second oxygen come from? Multiply bonded atoms such as this are found in alkenes, alkynes, carbonyls, and nitriles, and they require yet another rule.

5. If an atom is attached to another by a multiple bond (double or triple) both atoms are considered to be duplicated. The duplicated atom (X°) is considered to have a valence of zero and has a lower priority than a real atom (X), if that is the only point of difference.

This rule will convert the following common functional groups into their phantom counterparts for consideration in the priority scheme.

$$C^{*}-CH = CH_{2} \equiv C^{*}-C^{HCC^{\circ}}-C^{C^{\circ}HH}$$

$$C^{*}-C \equiv C-Me \equiv C^{*}-C^{CC^{\circ}C^{\circ}}-C^{CHHH}$$

$$C^{*}-C \equiv N \equiv C^{*}-C^{NN^{\circ}N^{\circ}}-N^{CC^{\circ}C^{\circ}}$$

$$C^{*}-C \equiv N \equiv C^{*}-C^{NN^{\circ}N^{\circ}}-N^{CC^{\circ}C^{\circ}}$$

Generally, both X° and X are simply treated as real atoms. If the only choice is between a duplicated atom X° and a real atom (X), however, the duplicated atom has a lower priority (in this case, all other rules have failed to establish the priorities). With the *tert*-butyl fragment, for example, proceeding down the chain to the first point of difference leads to *tert*-butyl with a lower priority than the alkynyl fragment:

C*-C=C-Me vs. C*-CMe₃ $C^{*-CC^{\circ}C} - C^{CC^{\circ}C} > C^{*-CC^{\circ}C} - C^{HHH}$

The C and C° are taken as equal in this analysis and rule 4 determines the priority. We compare $C^{CC°C}$ with C^{HHH} , giving the alkyl fragment a higher priority. Another example of this rule is the analysis of 6-methyl-hept-1-en-4-ol (**52**), which shows $O(a) > C \approx C > H(a)$. The alkenyl arm is C*-C^{CHH}-C^{CHC°} and the alkyl arm is C*-C^{CHH}-C^{CCH}. In this case the rules are unable to distinguish the priority of these two fragments. One proceeds to the next atom (C^{C°HH}), which is compared with C^{HHH} (=CH₂ vs. CH₃). The former atom is higher in priority and becomes group (*b*). The absolute configuration of **52** is (*S*).



The International Union of Pure and Applied Chemistry (IUPAC) Commission assembled a list of common substituents, sorted by increasing order of sequence rule preference (number 76, iodo, is the highest priority and number 1, hydrogen, is the lowest priority in that table).¹⁶ With this table two or more substituents can be evaluated in order to determine their relative priority using the CIP selection rules.¹⁷ Higher numbers have a higher priority. Iodo (76) has a higher priority than bromo (75) and hydrogen (1) has the lowest priority. Similarly, allyl (10) has a higher priority than propyl (4), acetylenyl (21, C=CH) has a higher priority than *tert*-butyl (19), and hydroxyl (57) has a higher priority than amino (43).



^{17.} Cahn, R.S. J. Chem. Educ. 1964, 41, 116.

In principle, a nitrogen atom can be stereogenic if there are three different alkyl groups on nitrogen (the fourth group is the lone pair of electrons on nitrogen). The nitrogen may be a stereogenic center, but rapid inversion at nitrogen leads to the mirror image (see 53) being present at the same time. Because of this facile racemization such compounds are not optically active unless this fluxional inversion can be inhibited. Approximately 2 x 10^{11} inversions occur each second for ammonia.¹⁸ The energy barrier for this inversion is somewhat higher in amines (see Table 1.3)²⁰ due the presence of alkyl groups on nitrogen that are bulkier than the hydrogens in ammonia. Nonetheless, alkyl amines undergo rapid inversion.¹⁹ The magnitude of the energy barrier to inversion in amines is determined by the inter-group bond angle (α , C1-N-C2), and the corresponding bending force constant.²⁰ Table 1.3²⁰ shows values of the parameter (α) for ammonia, trimethylamine, phosphine, and trimethylphosphine, along with an estimate for the energy barrier to inversion. Older estimates of these energy barriers are also included.²¹ The inversion at nitrogen in alkyl amines cannot be stopped at the reaction temperatures usually employed in organic chemical reactions. When inversion is impossible due to structural features of a molecule such as those found in bicyclic and polycyclic amines, the nitrogen is stereogenic and enantiomers are observed.

Compound	α	E _{inversion} (kcal mol ⁻¹)	Einversion (kJ mol ⁻¹)
NH ₃	106.77°	5.58 ^a	23.2 ^a
		11 ^b	46.0 ^b
PH ₃	93.3°	27 ^a	112.9 ^a
		47 ^b	196.5 ^b
NMe ₃	109.0°	7.46 ^a	31.2 ^a
		15 ^b	62.7 ^b
PMe ₃	100°	20.4 ^a	85.3 ^a
		57 ^b	283.3 ^b
^a Reference 20	^b Reference 21		
[Reprinted with permission from Koeppl, G.W.; Sagatys, D.S.; Krishnamurthy, G.S.; Miller, S.I.			
J. Am. Chem. Soc. 1967, 89, 5396. Copyright © 1967 American Chemical Society, and from Kincaid, J.F.; Henriques Jr., F.C. J. Am. Chem. Soc. 1940, 62, 1474. Copyright © 1940 American Chemical Society.]			

 Table 1.3.
 Energy Barrier to Inversion of Amines and Phosphines

^{18.} Smith, M.B.; March, J. March's Advanced Organic Chemistry, 6th ed., Wiley, New York, 2007, pp 142-144.

 ⁽a) Mislow, K. Pure Appl. Chem. 1968, 25, 549; (b) Rauk, A.; Allen, L.C.; Mislow, K. Angew. Chem. Int. Ed. 1970, 9, 400; (c) Lambert, J.B. Top. Stereochem. 1971, 6, 19.

^{20.} Koeppl, G.W.; Sagatys, D.S.; Krishnamurthy, G.S.; Miller, S.I. J. Am. Chem. Soc. 1967, 89, 3396.

^{21.} Kincaid, J.F.; Henriques, Jr., F.C. J. Am. Chem. Soc. 1940, 62, 1474.



The energy barrier for inversion is low for second row elements (C, O, N), and rapid inversion occurs. With elements in the third row (such as P and S), however, inversion is slow at ambient temperature and those molecules may exist as enantiomers. Methylphenylphosphine (**54**) is configurationally stable at 25°C, although it rapidly inverts at 130°C.^{22b} At 130°C, this barrier was measured to be 30.7 kcal mol⁻¹ (128.4 kJ mol⁻¹),^{22a} for a rate of inversion of 3.34 x 10⁵ s⁻¹.²² At 130°C, phosphine **55** showed a rate of inversion of 0.043 x 10⁵ s⁻¹ and the rate for **56** was 1.44 x 10⁵ s⁻¹ [E_a = 32.2 kcal mol⁻¹ (134.6 kJ mol⁻¹)].²³

If a nitrogen atom is a stereogenic center, it must be assigned a configuration by the CIP selection rules. An example is the bridgehead nitrogen in (–)-castoramine (**57**),²⁴ which is incapable of inversion at nitrogen because of its rigid bicyclic structure.²⁵ Castoramine is also drawn such that the *trans*-orientation of the electron pair is indicated, which is preferred to the *cis*- orientation by ≈ 2.4 kcal mol⁻¹ (10.0 kJ mol⁻¹).²⁵ This barrier effectively locks the molecule into the trans conformation. In this case, the electron pair must be considered a group but the first five rules do not allow it to be assigned a priority. A sixth rule is necessary.

6. Lone electron pairs receive an atomic number of zero and are assigned the lowest priority. The duplicated C, O and N atoms from rule 5 have a higher priority rather than an electron pair.

For (-) castoramine (57), rule 6 sets the priority such that the stereogenic nitrogen center is (*R*). Just as a nitrogen atom can be stereogenic, a phosphorus atom in a phosphine such as 54 can be considered chiral at temperatures up to about 130°C, as noted in Table 1.3. The lone pair electrons have the lowest priority by rule 6, and the absolute configuration is (*R*).

The six rules for determining the priority of groups on stereogenic centers can be applied to any molecule. Natural products are particularly interesting, since they are

 ⁽a) Horner, L.; Winkler, H.; Rapp, A.; Mentrup, A.; Hoffmann, H.; Beck, P. *Tetrahedron Lett.* 1961, 161; (b) Horner, L.; Winkler, H. *Ibid* 1964, 461.

^{23.} Baechler, R.D.; Mislow, K. J. Am. Chem. Soc. 1970, 92, 3090.

^{24.} LaLonde, R.T.; Muhammad, N.; Wong, C.F.; Sturiale, E.R. J. Org. Chem, 1980, 45, 3664.

^{25. (}a) Aaron H.S.; Ferguson, C.P Tetrahedron Lett. 1968, 6191; (b) Aaron H.S. Chem. Ind. (London) 1965, 1338.

the targets of many synthetic endeavors. As noted above, the absolute and relative configuration of such molecules must be known if they become synthetic targets, and this must be factored into the retrosynthetic plan. The *Amaryllidaceae* alkaloid crinine (58) has four stereogenic centers, including the ring-fused nitrogen atom. The absolute stereochemistry for each stereogenic center, as the molecule is drawn, is indicated where



each is treated as if it were an individual and isolated atom. In other words, focus on the carbon bearing the OH group, treat it as an individual tetrahedral carbon with four attached groups (independent of the fact they are all part of one molecule) and then assign priorities. Once done, that carbon atom is determined to have an absolute configuration of (R). This fundamental approach is used for all the stereogenic centers, and it can be applied to any molecule, regardless of the complexity. In some cases assigning priorities can be tedious and occasionally confusing, but there are rules to cover all contingencies.

The rules given above allow (R) or (S) configuration to be assigned for relatively simple molecules, and both 57 and 58 are included as a relatively simple molecule, but application to complex molecules can be problematic. Compound 59, for example, is non-trivial, and assigning all stereogenic centers by this manual method is at best time consuming, at worst difficult and prone to error. Modern computational methods, with algorithms to asses the absolute configuration, make such assignments rapid and rather easy. One simply draws the structure with the correct stereochemical relationships in the model, and the program makes the correct assignment. Indeed, the computergenerated assignments are shown in 59. Draw structures 60 and 61, and assign the absolute configuration using Spartan, and compare with the results that are given. Try it using the rules just discussed as well! Compound **60** is the oligocyclopropane FR-900848,²⁶ and **61** is the macrolide toxin pectenotoxin 2.²⁷ A similar analysis of the absolute configuration is shown for all stereogenic centers in ciguatoxin, **62**.²⁸



^{26.} Yoshida, M.; Ezaki, M.; Hashimoto, M.; Yamashita, M.; Shigematsu, N.; Okuhara, M.; Kohsaka, M.; Horikoshi, K. J. Antibiot. 1990, 43, 748.

 ⁽a) Yasumoto, T.; Murata, M.; Oshima, Y.; Sano, G. K.; Matsumoto, J. *Tetrahedron* 1985, 41, 1019; (b) Murata, M.; Sano, M.; Iwashita, T.; Naoki, H.; Yasumoto, T. *Agric. Biol. Chem.* 1986, 50, 2693; (c) Sasaki, K.; Wright, J.L.C.; Yasumoto, T. J. Org. Chem. 1998, 63, 2475; (d) Suzuki, T.; Beuzenberg, V.; Mackenzie, L.; Quilliam, M.A. J. Chromatogr. A 2003, 992, 141; (e) Miles, C.O.; Wilkins, A.L.; Samdal, I.A.; Sandvik, M.; Petersen, D.; Quilliam, M.A.; Naustvoll, L.J.; Rundberget, T.; Torgesen, T.; Hovgaard, P.; Jensen, D.J.; Cooney, J.M. Chem. Res. Toxicol. 2004, 17, 1423; (f) Halim, R.; Brimble, M.A.; Merten, J. Org. Lett. 2005, 7, 265.

 ⁽a) Scheuer, P.J.; Takahashi, W.; Tsutsumi, J.; Yoshida, T. Science 1967, 155, 1267; (b) Murata, M.; Legurand, A.M.; Ishibashi, Y.; Fukui, M.; Yasumoto, T. J. Am. Chem. Soc. 1990, 112, 4380; (c) Satake, M.; Morohashi, A.; Oguri, H.; Oishi, T.; Hirama, M.; Harada, N.; Yasumoto, T. J. Am. Chem. Soc. 1997, 119, 11325; (d) Hamajima, A.; Isobe, M. Org. Lett. 2006, 8, 1205.

1.4.B. Diastereomers

When there is more than one stereogenic center, the maximum number of possible stereoisomers is predicted by the 2^n rule (for *n* stereogenic centers there is a maximum of 2^n stereoisomers). Therefore, two stereogenic centers in a molecule such as **63** lead to four possible stereoisomers with the configurations C1(*R*)-C2(*R*), C1(*S*)-C2(*S*), C1(*R*)-C2(*S*) and C1(*S*)-C₂(*R*). Bromohydrin **63** has the configuration (*SS*), and its enantiomeric mirror image (**64**) is (*RR*). Similarly, the (RS) compound (**65**) and its mirror image (**66**) with the (*SR*) configuration are enantiomers. Comparison of **63** and **65** shows they are also stereoisomers, but they are *not* mirror images *nor* are they superimposable. This type of stereoisomer is given the name **diastereomer**: stereoisomers with two or more stereogenic centers that are not superimposable and not mirror images. By this definition, **64** and **66** are also diastereomers, as are **64** and **65** or **63** and **66**.



There are cases when a plane of symmetry bisects a diastereomer, as in *cis*-1,2-cyclopentanediol (67) and (2R,3S)-dibromobutane 68. The mirror image of (2R,3S)-dibromobutane is (2S,3R)-dibromobutane, the same compound. In effect, one half of the molecule is the mirror image of the other half as a result of the symmetry in the molecule, which leads to *fewer* stereoisomers than the maximum predicted by the 2^n rule. Structures 67 and 68 are superimposable upon their mirror images so *they are not enantiomers but are the same compound* and are called **meso compounds**. The cis-diol 67 is a meso compound but its diastereomer, the trans-diol, exists as enantiomers 69 and 70. There are a total of three stereoisomers: isomers 67 and 69 or 67 and 70 are diastereomers, 69 and 70 are enantiomers and 67 is a meso compound. Similarly, 67 is a meso compound, but 71 [(2S,3S)-dibromobutane] and 72 [(2R,3R)-dibromobutane]

are enantiomers giving the three stereoisomers. Note that changing the configuration of one stereogenic center $(2R \rightarrow 2S)$ cannot be done by rotation but only by making and breaking bonds. Dibromides **68** and **71** are diastereomers, as are **68** and **72**.

In chapters to come we will see that many different types of organic reactions produce diastereomers. These diastereomeric pairs show rotation about the carbon-carbon bond (see sec. 1.5.A), which precludes the configurational rigidity necessary for using the cisand trans-isomer designations. Separate nomenclature systems have been developed based on the relationship of the groups on the stereogenic centers. One system for distinguishing diastereomers labels them threo- and erythro. Unfortunately, there is more than one definition for threo- and erythro. Winstein and co-workers gave the following definition of these diastereomers: in a compound with two asymmetric carbons that has two common ligands and a third that differs, the isomers that would be meso if the third ligand were identical are erythro diastereomers.²⁹ An alternative definition is: if two asymmetric carbons have only one ligand in common, then the other four ligands are paired in the same commonsense way and isomers that would have equal pairs eclipsed in any conformation are erythro.³⁰ Eliel, Mislow and their co-workers³¹ defined erythro and threo in terms of Fischer projections. The aldol products (see sec. 9.4.A) **73** and **74**, and the ester-aldehyde condensation products **75** and **76**³² are shown with the erythro and threo notation.

To alleviate the confusion of the various uses and perceptions of the erythro/threo notation,³³ Masamune proposed the terms syn and anti to describe the relative stereochemistry of diastereomers.³⁴ In this notation, adjacent groups on the same side of an extended (zigzag) structure are syn, and those on opposite sides are anti. This model is illustrated with **77-79**.^{34,35} An extended structure is used as the basis of the model.

The clearest way to show differences is to use the absolute configuration (R) or (S) nomenclature for each stereogenic center in both enantiomers or in enantiomerically pure diastereomers. Throughout this book, the correct configuration will be cited or the synand anti-terminology will be used.

^{29.} Winstein, S.; Lucas, H.J. J. Am. Chem. Soc. 1939, 61, 1576, 2845.

^{30. (}a) Lucas H.J.; Schlatter, M.J.; Jones, R.C. J. Am. Chem. Soc. **1941**, 63, 22; (b) Cram, D.J. Ibid **1952**, 74, 2149; (c) Curtin, D.Y.; Kellom, D.B. Ibid **1953**, 75, 6011; (d) House, H.O. Ibid **1955**, 77, 5083.

 ⁽a) Eliel, E.L.; Wilen, S.H.; Mander, L.N. Stereochemistry of Organic Compounds, Wiley-Interscience, New York, 1994;
 (b) Eliel, E.L. Stereochemistry of Carbon Compounds, McGraw-Hill, New York, 1962;
 (c) Mislow, K. Introduction to Stereochemistry, W.A. Benjamin, New York, 1965.

^{32.} Meyers, A.I.; Reider, P.J. J. Am. Chem. Soc. 1979, 101, 2501.

^{33.} Seebach, D.; Prelog, V. Angew. Chem. Int. Ed. 1982, 21, 654.

^{34.} Masamune, S.; Ali, Sk.A.; Snitman, D.L.; Garvey, D.S. Angew. Chem. Int. Ed. 1980, 19, 557.

^{35.} Heathcock, C.H. in Asymmetric Synthesis, Vol. 3, Morrison, J.D. (Ed.), Academic Press, New York, 1984.

1.4.C. Chiral Molecules without a Stereogenic Center (Molecules Containing a Chiral Axis)

A few classes of organic molecules have a chiral axis although they do *not* have a stereogenic center.³⁶ The mirror image of such a molecule is not superimposable, *which means it is possible to have enantiomers without the presence of a stereogenic center*. Four important classes of compounds that exhibit this property are biaryls such as **80**, alkylidene cyclohexanes (**81**), substituted allenes such as **82** and substituted spiranes such as 3,9-diphenylspiro[5.5]tridecane (**83**).^{17,36} Chiral biaryls are important chiral catalysts and are used in many reactions



(see sec. 4.8.A, 4.9.G, and sec. 11.9). Obviously, it is important to determine the absolute configuration of both the chiral reactants and the asymmetric products resulting from their use. Allenes are common partners in pericyclic reactions (see secs. 11.4, 11.10 and 11.11) and they are chiral partners in some of these reactions. Alkylidene cyclohexanes are produced by phosphorus ylids upon reaction with cyclohexanone derivatives (see sec. 8.8.A) and the potential for creating asymmetric products is a key consideration in planning a synthesis of such compounds. However, no chiral atom is present and the CIP rules just described do not directly apply.



Chiral molecules that have no stereogenic center are evaluated by recognizing the presence of an extended tetrahedron (85A).³⁷ A normal tetrahedral atom is shown by 84, and if the bond lengths for atoms $a \rightarrow d$ were distorted to give an extended tetrahedron 85A would be obtained. Rather than a chiral atom, 85A contains a chiral axis, which can be used to assign priorities (see X---Y in 85B). This model requires that 85B not be interconvertible with its mirror image

^{36.} For a general discussion of this concept and molecules that exhibit this property, see Reference 12, pp 1119-1190.

^{37.} Reference 12, pp 1119-1122.

86 (i.e., rotation about the chiral axis X---Y must not interconvert **85** and **86**).

Allene 87 has a chiral axis since there are four different groups at each corner of the extended tetrahedron. These groups can be assigned priorities $a \rightarrow d$ (88A) by the usual rules, and a first glance suggests 88B (obtained by rotating 88A so the $a \rightarrow b \rightarrow c$ sequence is in front and the *d*-atom is to the rear) as the structure to be used for determining the absolute configuration. This is *incorrect*. There is nothing here to suggest the appropriate angle from which to view the extended tetrahedron. There is no C^*-C^d axis from which to view the molecule. The CIP rules were modified to accommodate an extended tetrahedron.¹⁷ (1) The top edge of the extended tetrahedron is prioritized a, b and the bottom edge of the extended tetrahedron is also prioritized a,b. (2) Near groups precede far groups when viewed from the top of the extended tetrahedron. With these rules, 87 is converted to 89 where the top a, b pair is associated with 1,2 (a = 1, b = 2). Similarly, the bottom a,b pair is assigned 3,4 (a = 3, b = 4) since top has priority over bottom. The model is rotated to put (4) to the rear and follows the order $1 \rightarrow 2$ \rightarrow 3 that gives a counterclockwise pathway and an (S) configuration. This new model can also be used with allene 90, where only two different groups are present. The methyl-hydrogen priorities are shown in 86 and converted to the $1 \rightarrow 4$ priority scheme, which places (4) to the rear, giving an (R) configuration.¹⁷ Molecules such as this can also be evaluated a priori using the Lowe-Brewster rules.³⁸ Eliel et al.³⁹ point out that the configuration of allenes and alkylidenecycloalkanes can be predicted by these rules in most case, but the model fails for many spirans.

$$\underset{k_{1}}{\overset{H}{\underset{k_{2}}}}{\overset{H}{\underset{k_{3}}}} = \underbrace{1}_{a} \underbrace{$$

Chiral axes occur for cyclic molecules containing an exocyclic alkylidene moiety such as **91**, which has two different groups at C4 of the cyclohexyl system and two different groups attached to the π bond. The C⁰⁰⁰ > H priority for CO₂H and H on the alkene is straightforward, and this constitutes the top of the extended tetrahedron. The cyclohexyl arms are in the plane of the π bond, but the methyl and hydrogen at C4 of the cyclohexane ring are in a different plane that constitutes the bottom of the extended tetrahedron. Since the methyl carbon has priority over the hydrogen the extended tetrahedron is **92A**, which leads to **92B** and the (*R*) configuration.¹⁷

^{38. (}a) Lowe, G. Chem. Commun. 1965, 411; (b) Brewster, J.H. Top. Stereochem. 1967, 2, 1; (c) Reference 12, pp 1129-1132.

^{39.} Reference 12, p 1091.



Biaryls such as **93A** can be analyzed with the extended tetrahedron model. The top aromatic ring is prioritized as *a,b* for the 2,6 substituents, as is the bottom ring (see **94A**). The near-far rule leads to **94B** and an (*R*) configuration.¹⁹ A reasonable question asks which aryl ring is on top and which is on the bottom of the extended tetrahedron. Do the rules accommodate these two orientations? Structure **93B** is identical to **93A** except the former has been rotated by 180°. Analysis of both structures leads to an (*R*) configuration. Prioritizing top and bottom *separately* accounts for rotating the molecule in this manner, but the top must be assigned *before* prioritizing the molecule and must *not* be changed after the process has begun. An example of a fused aromatic system used in synthesis is the reducing agent BINAL-H (an abbreviation for **95**, see sec. 4.8.A.).⁴⁰ The extended tetrahedron reveals an (*R*)-. Note that binding the aluminum atom into a ring, as shown in **95**, effectively locks the aromatic rings into a single configuration and does not allow racemization unless the C-C-C-Al-O- ring is disrupted.



^{40. (}a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. J. Am. Chem. Soc. **1984**, 106, 6709; (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *Ibid* **1984**, 106, 6717.

$$\begin{bmatrix} & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & &$$

1.4.D. (*E*/*Z*) Isomers

Alkenes can exist as stereoisomers. If asked to draw the structure of 3-hexene, two different molecules can be drawn (96 and 97). They are not superimposable, nor are they mirror images. Rotation is not possible around the C=C moiety, so the ethyl groups and the hydrogens have different spatial relationships. Those groups cannot be interconverted by rotation. Although no stereogenic center is present, 96 and 97 are stereoisomers and are formally considered to be diastereomers. In this particular case, the C=C unit has identical groups (ethyl) attached and the ethyl groups can be identified as being on the same side of the C=C or on opposite sides. When an alkene contains identical groups are on opposite sides, it is called a trans-alkene. Alkene 96 is *cis*-3-hexene and 97 is *trans*-3-hexene. These terms are part of the nomenclature as shown.

The terms cis and trans are applied in a straightforward manner for simple alkenes such as cisand trans-3-hexene or cis- and trans-1.2-dibromoethene. For 3-(1-bromo-1-methyl)-5hydroxy-4-(1-methylethyl)-hex-3-enoic acid (98), however, the cis-trans nomenclature does not apply. Which of the groups are used to determine sidedness? A more general nomenclature system is required, the (E/Z) system.^{17,41} The CIP selection rules are used for this system, to assign priorities to each carbon of the double bond. In 99, a and a' have the higher priorities and b and b' have the lower. Since a and a' are on the same side of the double bond, they are given the designation (Z) (from zusammen = together). Similarly, a and a' are on opposite sides in 100 and this arrangement is given the designation (E) (from entgegen = opposite). With this system, the hydroxyl-bearing carbon of C4 in 98 is assigned the highest priority (C^{CHO} vs. C^{CCH} for the isopropyl carbon). Analysis of C3 shows the bromine-bearing carbon to be the highest priority (C^{CCBr} vs. C^{CHH}). This is analogous to 100, and the name of 98 is (E)-(1-bromo-1methylethyl)- 5-hydroxy-4-(1-methylethyl)-hex-3-enoic acid. This nomenclature is generally applicable to all alkenes that do not have identical groups on one of the alkenyl carbons. 3-Hexene 96 is (Z)-3-hexene and 97 is (E)-3-hexene. The (E/Z) system will be used extensively throughout this book, but the cis/trans designations will be used for simple molecules and to describe relative stereochemistry. For example, the carbonyl group and the hydroxyl-bearing moiety in 98 are cis to each other.

^{41.} Reference 12, pp 541-543.



1.4.E. Prochiral Centers

There are molecules that do not possess a stereogenic center but generate a product with a stereogenic center after a chemical reaction. In terms of planning a reaction, it is important that we try to predict whether the product will have an (R)- or an (S)-configuration. To make this prediction, we must know from which face of the molecule the reagent will approach during the reaction. If it approaches from one face the (R)-enantiomer is generated; if it approaches from the opposite face the product is the (S)-enantiomer.

It is obvious that ketone 101 (2-butanone), and alkene 104 do not contain a stereogenic center. If 101 reacts with a Grignard reagent such as phenylmagnesium bromide (PhMgBr), however, the product is a racemic alcohol with enantiomers 102 and 103 (see sec. 8.4.C). Reaction of alkene 104 with a borane such as 9-BBN (9-borabicyclo[3.3.1]nonane) followed by oxidation gives a racemic alcohol, that is, enantiomers 105 and 106 (see sec. 5.4.A). In both cases, the reaction has produced a product that contains a stereogenic carbon. The ketone and alkene are described as prochiral,⁴² and a working definition of prochirality was provided by Hanson:⁴³ "If a chiral assembly is obtained when a point ligand in a finite non-chiral assembly of point ligands is replaced by a new point ligand, the original assembly is prochiral". A ligand is simply a group attached to the prochiral atom (a, b, c, d). A point ligand for a prochiral center has two characteristics: "(1) any two point ligands may be identical or non-identical, and (2)two point ligands may not occupy the same position in space."43 Addition of a point ligand to a prochiral center creates a new chiral center.⁴³ If the ligands are assigned a priority a-b-c-dby the CIP selection rules, configurations for each face of the prochiral center can be obtained. This rule is illustrated by conversion of the prochiral atom in 107 to either 108 or 109. In this example, 109 represents a (S) chiral center and is formed by replacement of a^{1} with b. Similarly, replacing a^2 generates a (R) chiral center 108. The a^1 and a^2 atoms are described by the terms **pro-S** and **pro-R**, respectively. A pro-R center is a point ligand in a prochiral molecule whose replacement leads to an (R) center. Analogously, a pro-S center is a point ligand in a prochiral molecule whose replacement leads to an (S) center. In 107, ligand a^2 is

^{42.} Reference 12, pp 465-488.

^{43.} Hanson, K.R. J. Am. Chem. Soc. 1966, 88, 2731.

pro-R and a^{1} is *pro-S*, and an example is D-glyceraldehyde **110**. The methylene group adjacent to the chiral center is prochiral, and replacement of H_b with a group X gives a (*S*) center in **111** (assuming X has a priority of *c* with H = *d*). Replacement of H_a gives a (*R*) center (in **112**) and that hydrogen is *pro-R*.



Hanson⁴³ described rules that accommodate most situations observed with prochiral centers. The reader is referred to this work for specific examples that do not yield to a simple analysis. The intent of this section is to familiarize the reader with nomenclature and the uses of *pro-R* and *pro-S* sites in reactions.



As noted above, synthetically important prochiral centers are the carbonyl of an unsymmetrical ketone or aldehyde and the double bond of an alkene. These functional groups do not contain a *pro-R* or *pro-S* group but it is clear that delivery of a fourth point ligand from one face or the other will lead to an (R) or (S) stereogenic center, as in conversion of **113** to **114** and/or **115**. If the carbonyl group is oriented as in ketone **116A**, priorities can be



assigned to the three atoms connected to the prochiral atom based on the CIP rules. For **116A**, the $a \rightarrow b \rightarrow c$ priority is counterclockwise and is analogous to (S). It is not really an (S) configuration, of course, since it is not a stereogenic center but this (S) sequence is termed *si*, from the Latin *sinister*.⁴³ When the incoming group approaches the π -bond from this face (with the orientation shown in **116A**) it is called the *si* face. If the molecule is given the opposite orientation, as in **116B**, the priority sequence $a \rightarrow b \rightarrow c$ is clockwise or (R) and this face is termed



re, from the Latin *rectus*. That face is the *re* face.⁴³ In this example, face *a* (see **116C**) is the *si* face and face *b* is the *re* face. Attack of hydride (see secs. 4.2.B, 4.7) from face *a* (the *si* face) leads to the (*R*) alcohol and attack from face *b* (the *re* face) leads to the (*S*) alcohol. The configuration of the final product depends on the priority of the new group added to the prochiral center.

Similar terminology can be applied to alkenes, as with (*Z*)-1-bromo-1-propene (117). In this case, there are two prochiral centers to be considered (C1 and C2 of the C=C bond), and *re* or *si* is assigned to each carbon. For 117, the top faces of both C1 and C2 are *re* (*re-re*) and the bottom faces are *si* (*si-si*)



1.4.F. Definitions of Selectivity

In the preceding sections various types of molecules were classified as regioisomers or stereoisomers (further categorized as diastereomers and enantiomers). When there are two different functional groups in a molecule, a given reagent may react preferentially with one rather than the other. Such a reaction is sometimes termed **chemoselective**. Oxidation of **118** with manganese dioxide (MnO₂, see sec. 3.2.F.iii) gave a 50% yield of **119** and 25% of **120**.⁴⁴ Manganese dioxide showed a preference for oxidation of the secondary allylic alcohol at the

^{44.} Hlubucek, J.R.; Hora, J.; Russell, S.W.; Toube, T.P.; Weedon, B.C.L. J. Chem. Soc. Perkin Trans. 1 1974, 848.



expense of the primary alcohol. The reagent selected one over the other, which leads to the term **chemoselective** (of two or more reactive functional groups, one reacted preferentially to give the major product in the mixture). When both products are formed but one is formed in greater proportions the term selective applies. Contrast this reaction with Gribble's reduction of ketoaldehyde **121** with tetrabutylammonium triacetoxyborohydride [Bu₄N⁺ BH(OAc)3⁻, where Ac = acetate and Bu = butyl, see sec. 4.5.A], to give **122** in 88%.⁴⁵ If the result had been different, and the aldehyde carbonyl was reduced and a portion of the ketone carbonyl was also reduced, the reaction would be chemoselective rather than chemospecific. If there had been 100% reduction of the aldehyde but 0% of the ketone, the reaction would be termed **chemospecific**. Trost defined these terms: "of two or more reactive functional groups, only

one reacts (specific), or one predominates (selective)". Reduction of alkenyl ketone **123** gave alcohol **124** and only the carbonyl reacts with sodium borohydride (NaBH₄). Since 0% of the alkene reacted, the reaction is chemospecific.



As noted above, the use of the terms selective and specific for giving a preponderance of a given product or only that product, respectively, can be applied for all reactions involving stereochemistry. If a reaction can produce two or more regioisomers, it is regioselective or regiospecific. The second order (E2) elimination (see sec. 2.9.A) of the racemic bromide **125** gave a mixture of **126** and **127** with **126** being the major product, so the reaction is regioselective. Elimination of the enantiopure (*S*,*S*)-diastereomer (**128**), however, gave *only* the (*Z*)-alkene **129** with none of the (*E*)-isomer and none of the alkene formed by removal the β -hydrogen on the methyl. The reaction is regiospecific and also stereospecific. This result was confirmed by reaction of the (*R*,*S*)-diastereomer **130** under E2 conditions, which gave only **131**. If **128** and **130** gave an unequal mixture of **129** and **131** the reaction would be stereoselective. One product is formed, so the reaction is stereospecific.

^{45.} Nutaitis, C.F.; Gribble, G.W. Tetrahedron Lett. 1983, 24, 4287.



Similar terminology is applied to formation of diastereomers. March and Smith⁴⁶ gave the example of maleic acid (132) and fumaric acid (134) and their reactions with bromine. On addition of bromine to 132, a racemic mixture of 133 was formed. Addition to 134 gave only *meso*-135. In both cases the reaction was diastereospecific. If 132 gave predominantly 133 with only a trace of the diastereomer (135), the reaction would be diastereoselective rather than diastereospecific.

The term stereoselectivity is applied to reaction products. If a reaction produces at least one substance that is not a stereoisomer of the major product, that reaction cannot be stereospecific but at most stereoselective.⁴⁷ If stereoisomeric starting materials react to give a single stereoisomeric product, the reaction is **stereospecific**, but if



another stereoisomerisalso produced (giving a mixture of products) the reaction is **stereoselective**. These terms apply to all types of stereoisomers, including enantiomers (**enantioselective** and **enantiospecific**), diastereomers (**diastereoselective** and **diastereospecific**) and regioisomers (**regioselective** and **regiospecific**). Reduction of keto ester **136** with zinc borohydride $[Zn(BH_4)_2$, see sec. 4.4.B and 4.7.B] gave 98% reduction with a >99:1 preference for **137** over **138**. The reaction produced two diastereomers, and it is **diastereoselective**.⁴⁷ Since traces of **138** are produced, the reduction cannot be diastereospecific.

^{46.} Reference 18, pp 1002.

^{47.} Oishi, T. in *New Synthetic Methodology and Functionally Interesting Compounds*, Yoshida, Z. (Ed.), Kodansha/Elsevier (Tokyo/Amsterdam), **1986**, pp 81-98.



The final definition concerns formation of enantiomers, and the terms enantioselective and enantiospecific are used. If a reaction produces an unequal mixture of enantiomers it is enantioselective. If it generates only one enantiomer of two possibilities it is **enantiospecific**. The baker's yeast reduction (see sec. 4.10.F) of **139** gave **140** with >99% ee (S).⁴⁸ (Here % ee means percent of **enantiomeric excess**.) A 0% ee means a 50:50 mixture (racemic mixture), 50% ee means a 75:25 mixture and 90% ee means a 95:5 mixture. The predominance of the (*S*) enantiomer makes this reaction highly enantioselective.



The selectivity terms introduced in this section will be used throughout the book for reactions that generate stereoisomers. In addition to % ee, % de (diastereomeric excess, defined in the same way as ee but for diastereomers), or % dr (diastereomeric ratio) will be used throughout.

1.5. CONFORMATIONS

Organic molecules can largely be categorized as having tetrahedral, trigonal or digonal (linear) geometry around each sp³, sp², or sp hybridized carbon atom, respectively. When organic molecules absorb energy from the environment they can partially dissipate excess energy by molecular vibrations, including rotation or twisting about all carbon-carbon single bonds. Generally, the more energy absorbed, the more facile will be the rotation. The three dimensional nature of carbon compounds, and rotation around carbon-carbon bonds leads to different spatial orientations of molecules called **rotamers**. Different rotamers are not different structures, but different orientations of the same molecule. Analysis of the spatial relationships of the groups can give information about the interactions of the groups as they rotate around the carbon-carbon bond. Based on these ideas, the shape that a molecule assumes is determined by understanding the rotamer population for all bonds, which leads to the overall shape (conformation) of the molecule. This shape is generally taken as the lowest energy **conformation** of that molecule. Most molecules have more than one conformation, but one or at least a small subset will constitute the low energy conformation(s). This information is

^{48.} Bolte, J.; Gourcy, J.-G.; Veschambre, H. Tetrahedron Lett. 1986, 27, 565.

used to determine how reagents will approach the molecule, and even the stereochemistry of certain reactions.

When we draw the structure of an acyclic molecule we usually draw the lowest energy rotamer, so we draw it with a regular shape rather than as an amorphous shape. For cyclic and polycyclic molecules the various interactions of the groups will lead to at least one and often several energy minima that are drawn to represent the shape of that molecule. In chemical reactions, the shape of the molecule will influence the way an incoming reagent interacts with it and this can have a significant effect on both reactivity and stereochemical induction, especially with the more rigid cyclic and polycyclic molecules. This section will discuss the fundamental conformational preferences of simple acyclic and cyclic molecules. These principles will be applied throughout the book for discussions of chemoselectivity and stereoselectivity.



An example of the link between conformation and stereochemistry is illustrated with bicyclic ketone **141**, which assumes a rigid structure so that a simple drawing is sufficient to conclude that one face is more encumbered than the other. It is, therefore, possible to anticipate the direction of hydride attack (see sec. 4.4.A) to be from the more open face of the molecule, from the direction of the arrow in **141** as it is drawn to give equatorial alcohol **142** as the only isomer isolated in 99% yield. This reaction was take from the total synthesis of the microbial immunosuppresive agent FR901483, by Weinreb and co-workers.⁴⁹ Acyclic molecules are problematic, however, since they do not assume a rigid conformation. They are quite flexible and all but the simplest molecules may exist in a variety of different shapes or conformations. Indeed, the shape of such molecules depends on the torsional angles involving the various single bonds. Generally, it is not possible to say which carbonyl face is likely to be the less crowded in a flexible ketone, and what the stereochemistry of a reaction product will be. The second example using ketone **143** is far more typical, where there are several possible conformations. Each has a different three-dimensional structure with different hindered or exposed regions. When **143**, taken from Jan and Liu's synthesis of (+)-ricciocarpin A, was

^{49.} Kropf, J.E.; Meigh, I.C.; Bebbington, M.W.P.; Weinreb, S.M. J. Org. Chem. 2006, 71, 2046.

reduced with NaBH4 (sec. 4.4.A), a 1:1.7 mixture of diastereomeric alcohols **144** and **145** was formed.⁵⁰ Even this relatively simple molecule shows enough conformational flexibility that a mixture of diastereomers is formed. In sec. 4.7.B, the Cram model and the Felkin-Ahn model will be discussed in order to predict selectivity in acyclic systems. However, both models assume that one key conformation is present in order to make the prediction. Identification of the "relevant" conformer or set of conformers is a necessary first step to anticipate product selectivity, and a conformational analysis is required.

1.5.A. Conformations of Acyclic Molecules

1.5.A.1. Conformations of Simple Alkanes

Different conformers result from rotation about single bonds and also from restricted rotations in rings. The number of different conformers depends on the number of single bonds and on the number and size of the flexible rings. A simple rule of thumb is that each single bond multiplies the number of possible conformers by three. Thus, a molecule with one single bond has three conformers, a molecule with two single bonds has nine conformers, and so forth. It is more difficult to elaborate conformers for flexible rings. Three-membered rings are conformationally rigid and four and (for the most part) five-membered rings can be considered to be rigid. Sixmembered rings comprising sp³ centers typically exhibit two "chair" conformers, although higher-energy "twist-boat" conformers are also possible. Seven-membered and larger rings generally posses an even grater number of conformers. In the final analysis, even a reasonably sized organic molecule can exhibit hundreds to thousands of possible conformations. Thus, identifying the relevant shape cannot be accomplished by simply looking at a single drawing or by simple manipulation of a model.

This section will introduce and illustrate computer-based conformational analysis tools. Properly used, these tools can furnish reliable predictions as to what shapes flexible molecules adopt and, in so doing provide insight into how they are likely to react. We start by introducing important conformational preferences established for organic molecules with only a single degree of conformational freedom. Our treatment relies heavily on data from quantum chemical calculations. This allows more detailed analysis than would otherwise be possible.



^{50.} Jan, N.-W.; Liu, H.-J. Org. Lett. 2006, 8, 151.

Ethane is a simple example of an acyclic molecule capable of rotation about two carbon atoms. If one could freeze this motion at different positions, the result would be different rotamers. Inspection of rotamer 146 and its Newman projection (the dot and circle model used in 148)⁸ reveals that the C-H bonds and the hydrogen atoms attached to each carbon are as far removed from each other as possible. Rotamer 147 (its Newman projection is 149) sharply contrasts with 146, since the C–H bonds and the hydrogen atoms attached to each carbon are as close together as possible. The traditional view is that non-bonded interaction between the two eclipsing hydrogens atoms and the electronic repulsion of the C-H bonds destabilizes this rotamer, making it higher in energy. Indeed, a review categorizes the destabilizing interactions as Pauli exchange steric repulsion, hyperconjugation, and relaxation energy changes.⁵¹ In addition, skeletal relaxation effects play a role.⁵¹ An analysis of ethane shows that the energy depends on the angle of torsion about the carbon-carbon bond. Complete (360°) rotation about the C–C bond (see Fig. 1.3) leads to three identical staggered structures (146A) that are energy minima and three identical eclipsed structures (148A) that are energy maxima. The difference in energy between the staggered and eclipsed structures is referred to as the barrier to rotation. At $\sim 12 \text{ kJ/mol}$,⁵² it is small enough that bond rotation will be very fast at normal temperatures.⁵³ This means that any measured properties for ethane actually represent an average of properties of the three (identical) conformers. The three (identical) eclipsed structures 148A do not contribute to the properties of ethane because they do not exist in the sense of contributing to the population.



Figure 1.3. Energy barrier for ethane over a rotation of 360°

Propane (150), with two identical carbon-carbon bonds, gives rise to nine identical energy minima and nine identical energy maxima. As with ethane, only the minima contribute to the

^{51.} Goodman, L.; Pophristic, V.; Weinhold, F. Acc. Chem. Res. 1999, 32, 983.

Measured at 2.9 kcal mol⁻¹ (12.1 kJ mol⁻¹):. (a) Gunstone, F.D. *Guidebook to Stereochemistry*, Longman, London, *1975*, p 56; (b) Reference 12, p 599; (c) Reference 29b, p 125 (d) Kagan, H. *Organic Stereochemistry*, Halsted Press/Wiley, New York, *1979*, p 50; (e) Hine, J. *Physical Organic Chemistry*, *2nd Ed.*, McGraw-Hill, New York, *1962*, p 36.

^{53.} The relative energies of conformers will be expressed in units of kJ mol⁻¹.

properties of the molecule. 2-Methylpropane (**151**) has three identical C–C bonds that give rise to 27 identical sets of energy minima and maxima, and 2,2-dimethylpropane (**152**) has four identical C–C bonds that give rise to 81 identical sets of energy minima and maxima. *Energy plots for all four molecules are identical, except for different rotational barriers*.



Butane has a new structural feature that must be addressed. The C1-C2 and the C3-C4 bonds are identical in terms of their substitution pattern, but the C2–C3 bond is different with each carbon having one methyl and two hydrogen atoms: H₃C–CH₂-CH₂-CH₃ versus H₃C-CH₂-CH₂-CH₃ (see **153A**). Rotation can occur about both C1–C2 and C3–C4, as seen by comparing **153A** and **153B**. Rotation of the central carbon-carbon bond in *n*-butane leads to three energy minima and three energy maxima, as indicated in Fig. 1.4. Two of the minima



Figure 1.4. Energy barrier for butane over a rotation of 360°

minima (so-called *gauche* conformers) are identical, while the third minimum (the so-called *anti* conformer) is different. Likewise, two of the energy maxima (connecting *gauche* and *anti* minima) are the same, while the third maximum (connecting the two *gauche* minima) is different. The magnitude of the barriers connecting *anti* and *gauche* conformers depends on the direction of rotation (*anti* to *gauche* or *gauche* to *anti*), the difference being the same as the energy difference between *anti* and *gauche n*-butane conformers. The maximum barrier to rotation is estimated to be 4.5-4.9 kcal mol⁻¹ (19-21 kJ mol⁻¹),⁵⁴ which represents the methyl-

^{54. (}a) Reference 52c; (b) Reference 52a, p 57; (c) Reference 12, p 602; (d) Reference 31b, p 126.

methyl interaction. The other energy barrier represents each Me-H eclipsing interaction and is estimated to be 3.6 kcal mol⁻¹ (15 kJ mol⁻¹).⁵⁵ The energy estimated for each *gauche* conformation is 0.96 kcal mol⁻¹ (4 kJ mol⁻¹),^{52b} an indication that the methyl groups are close but do not eclipse.

It is possible to categorize butane as a dimethyl substituted ethane. Energy profiles for rotation about the central carbon-carbon bond for a molecule such as 1,2-dichloroethane other disubstituted ethanes are qualitatively similar, in that each shows two *gauche* minima and one *anti* minimum (see Fig. 1.5). The relative energies of *gauche* and *anti* conformers and rotation barriers depend on the substituents. *Anti* conformers are usually preferred over *gauche* arrangements, for example, for 1,2-dichloroethane and for 1-chloropropane (**A** and **B** in Fig. 1.5, respectively). One reason for this preference is a desire to minimize unfavorable non-bonded contacts between the substituents. Another factor in some cases is electrostatics, the desire to align bond dipoles as to minimize the total dipole moment, for example, to align the $^{\delta+}C-F^{\delta-}$ bond dipoles in diffuoroethane such that they subtract rather than add.



Figure 1.5. Energy barrier for substituted ethanes over a rotation of 360°

1.5.A.2. The Boltzmann Distribution: Average Properties of Flexible Molecules

To obtain the properties of any sample of *n*-butane, it is necessary to average the properties of the *anti* and *gauche* conformers. More generally, to find the average value of a property (A) of a flexible molecule, it is necessary to sum over all possible different conformers, taking into account the value of the property for that conformer (a) as well as both the number of times that the conformer appears (n) and its Boltzmann weight (W).

$$\mathbf{A} = \sum \mathbf{a}_i \mathbf{n}_i \mathbf{W}_i$$

The Boltzmann weight depends on the energy of the conformer relative to the energy of the lowest energy conformer (ΔE), and on the temperature (T): $W_i = \exp(-\Delta E_i/kT) / \sum \exp(-\Delta E_i/kT)$ where k is the Boltzmann constant. An energy difference of 4 kJ mol⁻¹ leads to a Boltzmann

^{55. (}a) Reference 52a, p 57; (b) Reference 52c, pp 48-53.

weight of ~0.1 (10%) at room temperature, an energy difference of 1.9 kcal mol⁻¹ (8 kJ mol⁻¹) to a weight of ~0.05 (5%), and a difference of 12 kJ mol⁻¹ to a weight of ~0.01 (1%). Only rarely will more a few of the possible conformers have Boltzmann weights in excess of 1% and contribute significantly to the equilibrium. For molecules like ethane and propane where all conformers are the same, the average is independent of temperature. For *n*-butane, where the *anti* and the two equivalent *gauche* conformers contribute, the average depends on temperature. At very low temperatures, the average will be dominated by the lowest energy (*anti*) conformer, but it will limit to an equal weighting of both conformers as the temperature increases.

Note that measurements of some quantities, such as the NMR spectrum, yield averages over possible conformations while others such as the IR spectrum provide information about individual conformers. In the latter case, low Boltzmann weights will almost always preclude actually "seeing" any but the few lowest-energy conformers. Whether a particular measurement yields an average or discrete quantities depends on the time scale of the underlying physical process. Relaxation of magnetic spin (the basis of NMR) is typically slower than conformational equilibrium at normal temperatures, while molecular vibration (the basis of infrared spectroscopy) is much faster. The time scale of the experimental measurement must be established before interpreting the result.

Energy barriers for various molecules are quantified in terms of enthalpy (H^o), and calculation of the energy of a given rotamer allows an estimate the relative population of that rotamer (see Boltzmann distribution above). The relative energy of the conformations can be correlated with the relative percentage of each rotamer. An enthalpy difference of 1 kcal mol⁻¹ (4.186) kJ mol⁻¹) between the *anti* rotamer and the next most populous rotamer corresponds to the presence of about 72% of the anti-isomer at room temperature.⁵⁶ For butane, **154** is the all-anti conformation. The zigzag or extended look to conformation 154 is typically drawn to represent straight-chain alkanes. *n*-Tridecane (157), for example, is drawn as the all anti conformation, the extended conformation. Virtually all acyclic hydrocarbon chains are *assumed* to exist primarily in this conformation. This assumption is, of course, incorrect and conformer 157 probably does not exist to a significant extent in a real distribution. The previous discussion establishes that if butane exists in several conformations, the more flexible tridecane will exist in many more and we can use a Boltzmann distribution to estimate the contribution of different conformations. When drawing molecules, we usually draw straight-chain alkanes or alkyl fragments in this fully extended form. In reality, the conformational picture is much more complex and it is unlikely that molecules really look this way. This is a convention that is useful for drawing, but not for an analysis of chemical properties.

^{56. (}a) Reference 31b, pp 131-133.



1.5.A.3. Heteroatom Substituents

Thus far, discussion has concerned rotation about carbon-carbon bonds. The same principles apply to rotation about carbon-heteroatom bonds, particularly carbon-nitrogen and carbon-oxygen bonds. Consider methylamine and methanol. Different examples are methylamine and methanol. The nitrogen in organic amines is sp³ hybridized. Three of the hybrids form single bonds to other atoms while the fourth hybrid is thought of as a non-bonded pair of electrons (a lone pair). Similarly, the oxygen in alcohols or ethers is sp³ hybridized. In both cases, two of the hybrids are employed to bond to other atoms, leaving two lone pairs. This implies that both sp³ nitrogen and oxygen centers are roughly tetrahedral, consistent with the fact that nitrogen centers in amines are pyramidal and oxygen centers in alcohols and ethers are bent. Energy plots for methylamine (**A**) and methanol (**B**) are similar to that for ethane as seen in Fig. 1.6. All show three identical sets of energy minima and maxima. Rotational barriers are somewhat smaller than that in ethane: ~8 kJ mol⁻¹ in methylamine and ~4 kJ mol⁻¹ in methanol.



Figure 1.6. Energy barrier for substituted amines, alcohols, and ethers over a rotation of 360°

Substitution of a hydrogen on nitrogen in methylamine to give a secondary amine or on oxygen in methanol to give an ether, does not change the fundamental nature of the energy curves seen for the parent compounds, although it does change the details (energy barriers). On the other hand, substitution on carbon in both methylamine (to give ethylamine) and methanol (to give ethanol) leads to energy curves which, like that for *n*-butane, show two different minima (**C** for ethylamine in Fig. 1.6 and **D** for ethanol). Note that *anti-gauche* energy differences for both molecules are very small.



Groups capable of hydrogen bonding provide a stabilizing interaction that can compensate for the destabilizing interaction expected by steric repulsion. One can draw both an anti conformation (158) and a *syn*-conformation (159)

for 1,2-ethanediol (ethylene glycol), and the hydroxyl group is capable of hydrogen bonding. Rotating the molecule to the *gauche* conformation **160** relieves the eclipsing interaction but maintains the hydrogen bonding, making **160** the expected low-energy conformation *if no hydrogen-bonding solvent is present*. If the solvent is unable to hydrogen bond with ethylene glycol, the molecule will hydrogen bond with itself as shown. If the solvent can hydrogen bonding, and intermolecular hydrogen bonding will compete with intramolecular hydrogen bonding, and intermolecular hydrogen bonding will win on the basis of statistics (entropy).

Another way to stabilize an eclipsed or *gauche* conformation is to coordinate a heteroatom substituent with a metal ion (chelation). Oishi and co-worker's reduction of **161** with zinc borohydride proceeds via a chelated species, **162**.⁵⁷ Chelation of zinc



to the hydroxyl and carbonyl groups effectively immobilizes the reactive components into a single conformation in the transition state required for reaction, as shown in **162**. This fixed conformation sets the position of the methyl and hydrogen at the α -carbon, which leads to facial bias, and the hydride is delivered from the less hindered face over the hydrogen in **162** (see secs. 4.4.B and 4.7.B). Since transition metal salts usually behave as Lewis acids, the presence of a heteroatom that functions as a Lewis base (O, S, N, or P, see sec. 2.3) will lead to chelation. The most favored acyclic conformation is usually a *gauche* or analogous rotamer.

1.5.A.4. Heteroatom-Heteroatom Bonds

Many molecules have heteroatom-heteroatom bonds, such as N-N in hydrazines or O-O in peroxides. The energy profile for hydrazine (**163** in Fig. 1.7) is quite different from those of previous systems, containing two identical minima corresponding to arrangements in which the nitrogen lone pairs are perpendicular, and two different maxima. The higher maximum is \sim 44 kJ mol⁻¹ above the minima and corresponds to an arrangement in which both NH bonds eclipse

^{57.} Nakata, T.; Tanaka, T.; Oishi, T. Tetrahedron Lett. 1983, 26, 2653.

and the two lone pairs eclipse. The other maximum is only 13 kJ mol⁻¹ above the minima and is very broad. It corresponds to a range of conformers centered around a structure in which the two lone pairs are *anti* to each other. Unfavorable lone pair-lone pair interactions are much larger than bond-bond or bond-lone-pair interactions even if the lone pairs point away from each other. The best way to minimize them is to keep the lone pairs perpendicular. Note that the preference due to lone pair interactions. Hydrogen peroxide provides another example of the consequences of interaction of lone pairs. The curve (**164** in Fig. 1.7) shows a pair of identical minima with torsional angles around 120° and 240°. The curve shows two different maxima. The higher is ~40 kJ mol⁻¹ above the minima and corresponds to a *syn* conformer (HOOH angle = 0°), while the lower is ~5 kJ mol⁻¹ above the minima and corresponds to an *anti* conformer (HOOH angle = 180°). In summary, hydrazine and hydrogen peroxide, like ethane, methylamine and methanol, are both described in terms of a single structure.



Figure 1.7. Energy barrier for substituted amines, alcohols, and ethers over a rotation of 360°

1.5.A.5. Bonds Connecting sp³ and sp² Hybrids: Propene and 1-Butene

The planar sp² carbon atoms in alkenes are relatively easy to distinguish, but what effect does the C=C unit have on the adjacent sp³–sp² bond? A plot of energy versus the C=C-C-H torsional angle in propene (**A** in Fig. 1.8) shows three identical minima and three identical maxima, just like that for ethane. Even the rotation barrier is similar (~8 kJ mol⁻¹ in propene versus ~12 kJ mol⁻¹ in ethane). However, the methyl group in propene sees a different environment than the methyl group in ethane. If it staggers the vinylic C-H bond, then it must eclipse the C=C unit and vice versa. The minima in propene correspond to arrangements in which one of the methyl C-H bonds eclipse the carbon-carbon double bond but two methyl carbons stagger the alkene C-H bond. The plot for the central carbon-carbon single bond in 1-butene (**B** in Fig. 1.8) closely resembles the corresponding curve for *n*-butane. It shows three minima, two that are identical corresponding to arrangements in which a (methylene) C-H bond eclipses the carbon-carbon double bond, and the third only ~3 kJ mol⁻¹ higher in energy in which the C–C
single bond eclipses the double bond. There is a general rule that single bonds eclipse double bonds.



Figure 1.8. Rotation of propene and butene about 360°



Much larger conformational preferences involving single and double bonds can occur. The most conspicuous are the C-O bonds in carboxylic acids and carboxylic acid esters, between sp² (carbonyl group) and sp³ (oxygen) centers. Energy curves for CO bond rotation in acetic acid and in methyl acetate (**A** and **B**, respectively, in Fig. 1.9) both show two minima corresponding to *syn* (O=CCH and O=CCC = 0°) and *anti* (O=CCH and O=CCC = 180°) arrangements, and a pair of identical maxima in between. The *syn* conformer is preferred by nearly 60 kJ mol⁻¹ for both molecules. In both conformers, C=O and O-H (O-Me) bonds eclipse but the C=O and C–O bond dipoles subtract in the *syn*-conformer and they add in the *anti*-conformer (see **A** and **B**).



Figure 1.9. Rotation of propene and butene about 360°

1.5.A.6. Bonds Connecting sp² Hybrids: 1,3-Butadiene and Styrene

A final case is presented that focuses on the carbon-carbon single bond connecting two sp² hybridized atoms, such as those found in conjugated dienes or styrene derivatives. The conventional wisdom is that the two double bonds need to be coplanar in order to maximize "conjugation". While trans planar 1,3-butadiene is an energy minimum, the corresponding cis planar conformer is not (see A in Fig. 1.10). There is an energy minimum nearby (CCCC torsion angle ~40°) that is ~12 kJ mol⁻¹ higher than a cis form (an energy maximum), and ~12 kJ mol⁻¹ higher in energy than the *trans* form. The energy barrier to rotation about C_2 - C_3 has been shown to be 5 kcal mol⁻¹ (21 kJ mol⁻¹).⁵⁸ The two rotamers mentioned arise by rotation about the C₂-C₃ single bond: 165 with the two π bonds cis- to each other and 166 with the π -bonds trans. Rotamer 165 is called the s-cis conformation, and 166 is the s-trans-conformation. When the diene is substituted, (E,E)-, (Z,E)- and (E,Z)- dienes are possible. The s-cis conformation of (Z,Z)-3,5-hexadiene (167) is even less favorable than the s-trans conformation (168), when compared with 1,3-butadiene. In 167, the Me-Me interaction is guite apparent, and although the s-trans conformer (168) has two methyl-hydrogen interactions, it is lower in energy than the Me-Me interaction in 167.



Figure 1.10. Rotation of propene and butene about 360°

^{58.} Reference 52c, p 54.

Similar expectations apply to styrene (see **B** in Fig. 1.10) where there is only one unique conformer. Here the vinyl and phenyl groups are nearly coplanar and the energy barrier through planar styrene is tiny. With the advent of coupling reactions such as the Heck reaction (sec. 12.7.A), such compounds have gained greater importance.



1.5.B. Conformations of Cyclic Molecules

Steric and electronic interactions influence the rotation about bonds within acyclic molecules, leading to a relatively small population of low-energy rotamers. The cyclic nature of these molecules imposes additional energy barriers to conformational mobility relative to acyclic molecules. Although the C–C bonds in cyclic compounds are not capable of complete rotation, they undergo what is known as pseudorotation, largely by twisting and bending around the various carbon-carbon bonds in the ring. Depending on the flexibility of the ring, which is related to the size of the ring, many conformations are possible. As with acyclic compounds, there are usually a small number of low energy conformation that dominate the population.

An important difference that is observed in cyclic molecules is deformation of the bond angles from 109°28' as the molecule attempts to rotate around the C-C bonds, which can be severe when the ring is small. Cyclopropane, for example, has a C-C-C bond angle of $\sim 60^{\circ}$ (see 169) which induces great strain in the molecule. This type of strain is called **Baeyer** or angle strain, formally defined as the increase in energy of cyclic compounds that arises from the deformation of the optimum valence angle of 109°28' for sp³ carbon or 120° for sp² carbon. The higher ground state energy for cyclopropane is the result of such strain. Formation of threemembered rings is common, but the higher ground state energy is important in the reactions of cyclopropane as well as those that form cyclopropanes.⁵⁸ Deformation of the σ bonds leads to significant p character (the hybridization is Csp^{2·3}), and many ring-opening reactions of cyclopropane mimic the chemistry of alkenes. The increased p-character is reflected in the diminished electron density of the C-C bonds in cyclopropane, which is slightly displaced from linearity between the nuclei.⁵⁹ The four-carbon cyclic compound is cyclobutane (see 170) with bond angles of ~90°, and in planar cyclopentane (171A) with bond angles of $\sim 108^{\circ}$. Cyclobutane has significant Baeyer strain, less than in cyclopropane but more than in cyclopentane.

^{59. (}a) Bernett, W.A. J. Chem. Educ. 1967, 44, 17; (b) de Meijere, A. Angew. Chem. Int. Ed. 1979, 18, 809; (c) Reference 12, pp 676-678; (d) Reference 31b, pp 204-306 and 124-179.

Cyclopropane (169), planar cyclobutane (170A) and planar cyclopentane (171A) exhibit a second major type of strain, which is the same as that seen in acyclic molecules. All C-H bonds in these planar molecules are eclipsed, with severe nonbonded interactions of the eclipsed hydrogens and electronic repulsion of the eclipsed bonds. This type of strain is called **Pitzer** or **bond opposition strain** and is defined as the increase in energy for a compound arising when adjacent bonds are eclipsed, bringing the attached atoms into close spatial proximity. Cyclic molecules generally do not exist in the planar form due to the Pitzer strain. Although rotation of 360° about the C-C bonds is not possible, twisting and bending is possible via partial rotation (pseudorotation) to minimize Pitzer strain.⁵⁹ One or two low-energy conformations are usually drawn to represent the entire molecule, although as the ring becomes larger and the flexibility increases more low energy conformations are possible. For cyclobutane, a bent or puckered conformation (170B) is taken as the low energy conformation,⁶⁰ which minimizes Baeyer strain relative to the planar form (170A).⁶¹ For cyclopentane, the bent conformation assumes an envelope shape as in 171B.⁶¹ Although Baeyer strain is increased in the envelope conformation (171B) relative to the planar form (171A),⁶² the decrease in Pitzer strain more than compensates and 171B is the low-energy conformation of cyclopentane. Analysis of planar cyclohexane (172A) reveals extensive Pitzer strain and the bond angles would be 120°, introducing Baever strain. Pseudorotation leads to the familiar chair conformation (172B) as the low energy conformation. Chair cyclohexane has virtually no Baeyer strain with bond angles of 109°28'. Cycloheptane has similar bond angles⁶³ but is more flexible, and there are several low energy conformations, although only 173A is shown. Cycloheptane also has a boatform (173B) that is very close in energy to a chair form 173A.⁶⁴ The lowest energy form of cycloheptane, however, is the twist-chair conformation, 173C.65



- 60. (a) Reference 12, p 676; (b) Reference 31b, p 248.
- 61. (a) Dunitz, J.D.; Schomaker, V. J. Chem. Phys. 1952, 20, 1703; (b) Rathjens, Jr., G.W.; Freeman, N.K.; Gwinn, W.D.; Pitzer, K.S. J. Am. Chem. Soc. 1953, 75, 5634.
- 62. Kilpatrick, J.E.; Pitzer, K.S.; Spitzer, R. J. Am. Chem. Soc. 1947, 69, 2483.
- 63. (a) Reference 12, pp 686-689; (b) Reference 29b, p 252.
- 64. Allinger, N.L. J. Am. Chem. Soc. 1959, 81, 5727.
- 65. Wiberg, K.B. J. Org. Chem. 2003, 68, 9322.



As mentioned, cyclohexane is known to favor a "chair" structure in which all six carbons are equivalent but the hydrogens divide into two sets of six *equatorial* hydrogens and six *axial* hydrogens, marked in **178**. However, the fact that only one proton resonance is seen in its room temperature NMR spectrum suggests a rapid conformation change in which *equatorial* and *axial* hydrogens exchange. An energy profile for the process (Fig.1.11) shows the two identical chair structures as the starting and ending points, respectively, marked **178** and **179**. There is a boat conformation (**175**), as well as two identical higher-energy "twist-boat" minima (**176**). In **175**, there is a cross ring (**transannular**) interaction of the 1,4-hydrogens (referred to as flagpole hydrogens). The curve contains three energy maxima. Two are identical "half chairs" (**177**) and connect the chair a twist boat forms, while the boat (**175**) connects the two twist-boat forms.



Figure. 1.11. Conformational mobility of cyclohexane.



Chair cyclohexane is $\sim 28 \text{ kJ mol}^{-1}$ lower in energy than the twist-boat (or just twist) conformation, suggesting that the latter will have little influence on the properties of cyclohexane. It is not possible to attach a simple label

to the geometrical coordinate in Fig. 1.11 responsible for this process. However, interconversion of chair cyclohexane into the twist-boat form can be viewed as a restricted rotation about one of the ring bonds (see **180** to **181**). Correspondingly, the interconversion of the twist-boat intermediate into the other chair form can be viewed as rotation about the opposite ring bond.

The molecular conformations induced by relief of Baeyer strain and Pitzer strain are reflected in the energy required for intramolecular cyclization reactions to form each ring. As two reactive ends of the acyclic fragment come together, the strain inherent to the ring product becomes important (see sec. 6.6.B.i). In other words, the acyclic precursor assumes the conformation of the ring that is being formed in the transition state of the reaction. Strain in this transition state is important for the formation of the cyclic product. Figure 1.12(a) shows the relative

reactivity for formation of lactones from ω -hydroxy acids of ring size C3 to C17.⁶⁶ There is a reactivity maximum at C5 and reactivity minima at C3 and C8.⁶⁶ Figure 1.12(b) shows the enthalpy (Δ H) of several cyclic alkanes, with a minimum at C6 and a maximum at C9.⁶⁷ There are two other important features of Figure 1.12 (b). Rings of C8-C13 members are significantly higher in energy than the small rings (C3 \rightarrow C7) or the large rings (\geq C14). These medium size rings are extremely difficult to form using intramolecular cyclization.⁶⁶ The other feature of Figure 1.12(b) is the higher energy required to form rings with an odd number of atoms when compared to the energy required to form rings with an even number of atoms. Compare cyclohexane and cycloheptane to see the difference. Cycloheptane has an odd carbon that is not easily accommodated by the low-energy chair (all *gauche*) form, and its presence leads to an increase in Pitzer strain.^{67,66} Similar effects are seen for all odd carbon rings.



Figure 1.12. (a) Reactivity Profile for Lactone Formation. (b) Enthalpy of Cycloalkanes [CnH2n]. [Reprinted with permission from Illuminati, G.; Mandolini, L. Acc. Chem. Res. 1981, 14, 95. Copyright © 1981 American Chemical Society.]

As the ring size increases to eight members and higher, increased flexibility leads to an increasing number of lower energy conformations. Indeed, an inspection of cyclooctane reveals there are several conformations, including **174B** (crown), **174C** (boat-chair), a boat-boat conformation (**174D**)^{68,64} as well as twist-boat-chair and twist chair-chair conformations.⁶⁹ These latter conformations are higher in energy than the crown (**174B**).⁷⁰ Wiberg used calculations to show that the boat-chair is the lowest energy conformer, with the twist boat-chair, twist chair-chair and the crown as the next higher energy conformations.⁶⁴ The boat-conformation is relatively high in energy.⁶⁴ A crown conformation is observed for cyclodecane, **182A**,^{67b,71}

- 68. Bellis, H.E.; Slowinski, E.J. Spectrochim. Acta 1959, 15, 1103;
- 69. Pauncz, R.; Ginsburg, D. Tetrahedron 1960, 9, 40.

71. Prelog, V. J. Chem. Soc. 1950, 420.

^{66.} Illuminati, G.; Mandolini, L. Acc. Chem. Res. 1981, 14, 95. Also see Ref. 12, p 680.

^{67.} Also see (a) Dunitz, J.D.; Prelog, V.P Angew. Chem. 1960, 72, 896; (b) Prelog, V. in Perspectives in Organic Chemistry, Todd, A.R. (Ed.), Interscience, New York, 1956, p 96.

^{70. (}a) Reference 12, pp 765-766; (b) Reference 31b, p 253; (c) Allinger, N.L.; Hu, S. J. Am. Chem. Soc. 1961, 83, 1664.



which conforms to the same extended chair conformation found in diamond (see Fig. 1.13). Crown-cyclodecane⁶⁴ fits on this diamond lattice⁶⁸ and it is usually taken as an important low energy conformation. The odd-membered ring in cyclononane shows a twist, also found in cycloheptane when compared to chair cyclohexane⁶⁰ and a slight increase in Pitzer strain. As seen in Figure 1.5, the twist in crown-like cyclononane makes it unable to superimpose on the diamond lattice. Even large rings such as cyclooctadecane can show this chair-like or crown-like conformation in a low energy form.



Figure 1.13. Cyclodecane and Cycloundecane on a Diamond Lattice.

Another type of strain that is found in large ring compounds must be introduced To better see this interaction, models of cyclopentane-cyclooctadecane are shown looking down on the top of each ring, exposing a cavity in the center of each ring. If the conformation of a ring brings atoms in close proximity, *within the cavity of the ring*, this is known as a **transannular interaction**.⁶⁶ Hydrogen atoms do not intrude into the internal cavities of envelope cyclopentane (**171C**) or chair cyclohexane (see **172C**), so there are no transannular interactions. In cycloheptane (see **173D**), two of the hydrogen atoms can move into positions that are slightly within the cavity,



contributing to modest transannular strain and partially accounting for the higher energy of cycloheptane. In crown-cyclooctane (174E), pseudorotation moves hydrogen atoms that are on opposite sides of the ring into the cavity, contributing to a significant transannular interaction, and a significant increase in the inherent energy for that ring. There is also significant transannular

strain in cyclononane (183) and crown-cyclodecane (182B). As the ring size increases, the cavity becomes larger, and the net energy decreases after reaching a maximum at cyclodecane. Although the potential for a transannular interaction is quite high in cyclooctadecane (184), the large cavity and increased flexibility allow the transannular hydrogens to sweep past each other upon pseudorotation. The cavity inside the ring is large enough to accommodate these atoms without generating a large energy gradient.



As shown above, the higher energy of medium size rings results from unfavorable dihedral angles.⁷¹ This type of strain has been termed *I-strain* (internal strain).⁷² Formally, *I strain* involves the change in strain when going from a tetrahedral to a trigonal carbon or vice versa (as in changing an alcohol to a ketone). For medium-size rings, tetrahedral bond angles bring the transannular substituents into close proximity. Conversion to a trigonal planar carbon relieves this interaction somewhat and lowers the energy of the system.⁷³ An example is the oxidation of cyclooctanol (**185**) to cyclooctanone (**186**, see sec. 3.2.A). The reverse process (the reduction, see secs. 4.2.B, 4.8.C, 4.9.B: **186 (B 185)**) is more difficult due to the increased *I* strain as well as increased transannular strain in the alcohol.⁷⁴



The presence of a heteroatom, a C=C unit, or a carbonyl influences the conformation of medium-size rings, but the changes are often subtle. The calculated low-energy conformation of cyclooctane (187) is compared with those of *cis*-cyclooctene (188), the ether oxocane (189) and cyclooctanone (190). Although 188 is somewhat flattened, the conformations of the other three eight-membered rings are rather similar.⁷⁵

^{72. (}a) Brown, H.C.; Fletcher, R.S.; Johannesen, R.B. J. Am. Chem. Soc. 1951, 73, 212; (b) Brown, H.C.; Borkowski, M. Ibid 1952, 74, 1894.

^{73.} Prelog, V. Bull. Chim. Soc. Fr. 1960, 1433.

^{74.} Reference 31b, pp 266-269.

^{75.} Pawar, D.M.; Moody, E.M.; Noe, E.A. J. Org. Chem. 1999, 64, 4586.



Estimating the conformations of large ring compounds (macrocycles) is more complicated, and more difficult than with compounds discussed in the section 1.4. Since this class of compounds includes macrolide antibiotics,^{76a} important commercial products such as muscone and also crown ethers,^{76b} there is a great deal of interest in macrocycles.⁷⁶ Both the chemical and physical properties of macrocycles depend on the conformations of the large ring.⁷⁷ An analysis of conformations of small and medium ring compounds was reported that used an analysis of the sign of torsional angles,⁷⁸ and when combined with the use of dihedral maps.⁷⁹ Weiler⁸⁰ produced a **polar map analysis** of macrocycles that yielded conformational information. This method has also been applied to the conformational analysis of macrocyclic ethers.⁸¹ Another way to represent this conformation is based on Dale's numerical system describing the number of bonds found between corner atoms.^{82c} Dale's system is sometimes called wedge notation.⁸³ Unfortunately, calculations can be difficult, and the method does not seem to be widely used. The system is based on the idea that even-membered rings can exist in four quadrangular (fourcornered system) conformations (see 191). (1) All four sides contain an odd number of bonds (a-d = odd). (2) Two adjacent sides are odd with the others even (ab odd, cd even; or bc odd, ad even). (3) Two adjacent sides are odd with the others even (ac odd, bd even; or bd odd, ac even). (4) All sides contain an even number of bonds ($a \rightarrow d = even$). For odd membered rings, the best conformation arises when there are three (a triangular system) or five corners (a quinguangular system). When there are three corners all three sets can be odd, or two can be even with one odd and one side must have one or more convex faces. For five corners, all can be odd, two adjacent or next to adjacent can be even with the other three odd, or one can be odd and four even, so there must be one or more concave faces.

^{76. (}a) Paterson, I.; Mansuri, M.M. *Tetrahedron* **1985**, *41*, 3568; (b) Hayward, R.C. Chem. Soc. Rev. 1983, 12, 285; (c) Still, W.C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981 and references cited therein.

^{77. (}a) Dale, J. Angew. Chem. Int. Ed. 1966, 5, 1000; (b) Idem Top Stereochem. 1976, 9, 199; (c) Idem Acta Chem. Scand. 1973, 27, 1115.

 ⁽a) Bucourt, R. Top Stereochem. 1974, 8, 159; (b) DeClerq, P.J. Tetrahedron 1984, 40, 3729; (c) Idem Ibid 1981, 37, 4277; (d) Toromanoff, E. Ibid 1980, 36, 2809.

^{79.} Ogura, H.; Furuhata, K.; Harada, Y.; Iitaka, Y. J. Am. Chem. Soc. 1978, 100, 6733.

 ⁽a) Ounsworth, J.P.; Weiler, L. J. Chem. Educ. 1987, 64, 568; (b) Keller, T.H.; Neeland, E.G.; Rettig, S.; Trotter, J.; Weiler, L. J. Am. Chem. Soc. 1988, 110, 7858.

^{81.} Clyne, D.S.; Weiler, L. Tetrahedron 2000, 56, 1281.

 ⁽a) Dale, J. Acta Chem. Scand. 1973, 27, 1115, 1130; (b) Dale, J. Acta Chem. Scand. 1973, 27, 1149; (c) Björnstad, S.L.; Borgen, G.; Dale, J.; Gaupset, G. Acta Chem. Scand. Ser. B 1975, B29, 320.

^{83.} Reference 12, pp 763-764, 766-769.



The actual notation is illustrated for the diamond form of cyclodecane, **192** (see Fig. 1.13). The dihedral angles were measured from a Dreiding ModelTM (this can also be done with appropriate computer software), and the corners determined for a given conformation. For 192, those angles for the four corners are +55/+80 and -55/-80. This method takes the number of bonds on each side, starting with the short side and gives the lowest possible combination of numbers. For **192**, there are 2, 3, 2 and 3 bonds, respectively, and this is [2323]-decane. Nonane has an odd number of atoms, and has three corners. Conformation 193 represents nonane and it has three corners with angles determined to be +55/+55, leading to the notation [333]nonane. For cyclotetradecane, the lowest energy conformation is 194, the [3434] conformation. When substituents are attached to large rings, they tend to occupy only exterior positions to minimize the large transannular interactions.⁸⁴ A fully substituted atom of a macrocycle will usually occupy a corner position since this is the only position where it does not cause severe transannular strain.⁸² For both substituted and unsubstituted macrocycles, the conformation of the ring will impose restraints on the torsional angles available to each unit of carbons (four carbons define a torsional angle). The use of polar maps of torsional angles may be of value for determining the conformation of many macrocyclic compounds. Fourteen-membered 3keto lactones, for example, have been synthesized and their conformations analyzed using this technique.⁸⁵ This ability to predict conformational bias is important to the stereochemical outcome of chemical reactions involving macrocyclic rings.

1.5.C. Estimating Conformational Populations

The preceding discussion focused on a low-energy conformation of several ring compounds, but in fact there may be several conformations for each ring that lie close together in energy. To obtain a complete picture several conformations of equal, close, or higher energy must be considered. The conformational mobility of cyclohexane includes, for example, the two low-energy chair conformations, six degenerate twist-boat conformations, and six degenerate

^{84.} Dale, J. Stereochemistry and Conformational Analysis, Verlag-Chemie, New York, 1978.

^{85.} Neeland, E.G.; Ounsworth, J.P.; Sims, R.J.; Weiler, L. J. Org. Chem. 1994, 59, 7383.

boat conformations.^{86,87} If all the energies for the various conformations are known, it should be possible to estimate the percent of each. Since the chair conformation usually constitutes the majority of this conformer population, a typical assumption is usually be made to ignore the other conformations for an initial estimation. Building cyclohexane using Spartan and minimizing the structure will generate a chair cyclohexane. Eliel et al.⁸⁸ estimated that the energy difference between the boat and chair forms is about 4 kcal mol⁻¹ (16 kJ mol⁻¹), which means "only one molecule in a thousand will be in the boat form" at 298 K (25°C). Note that the boat form exists in certain bridged cyclohexane molecules such as bicyclo[2.2.2]-octane (**195**) which is all boat, or it may be forced on the ring by bulky substituents (e.g., *trans*-1,2-di*tert*-butylcyclohexane) which contains about 12% of the boat **196A**.^{88,89}



The discussions of cyclohexane given above have made it clear that the chair conformations are lower in energy. The boat and two chair conformations are shown for **196** (trans-1,2di-tert-butylcyclohexane). It is clear that there are significant steric interactions in the boat (191A) because the two *tert*-butyl groups are in close proximity, whereas in the diaxial chair (196B) those groups are on opposite sides of the ring. Interestingly, the interaction of the tert-butyl groups is somewhat relieved in the twist-boat conformation, which exists alongside the more stable **196A**.⁸⁸ but the structures shown indicate that **196C** (the *tert*-butyl groups are both equatorial) is lower in energy than **196B** (the *tert*-butyl groups are both axial). Why is **196B** higher in energy than **196C**, and why is the low energy form the boat conformation 196A or the twist-boat conformation mentioned? The answer reveals two major sources of strain in chair cyclohexanes, which have both axial and equatorial bonds (see 178 and 179). In cyclohexane, this interaction of the axial hydrogen atoms on either side of the ring is minimal because hydrogen atoms are relatively small as seen in the space filling model 172D. Replacing the hydrogen atoms in the axial positions with substituents leads to competition for the space above and below the ring, giving rise to a transannular interaction (A strain, or $A^{1,3}$ -strain, a 1,3-diaxial interaction, see Fig. 1.14). When one hydrogen is replaced with a methyl group (methylcyclohexane, 197), the interaction between methyl and hydrogen is

 ⁽a) Lowry, T.H.; Richardson, K.S. Mechanism and Theory in Organic Chemistry, 3rd Ed., Harper and Row, New York, 1987, p 141; (b) Squillacote, M.; Sheriden, R.S.; Chapman, O.L.; Anet, F.A.L. J. Am. Chem. Soc. 1975, 97, 3244; (c) Hirsch, J.A. Concepts in Theoretical Organic Chemistry, Allyn and Bacon, Boston, 1974, pp 249-252.

^{87.} Barton, D.H.R. Experientia 1950, 6, 316.

^{88.} van de Graaf, B.; Baas, J.M.A.; Wepster, B.M. Recueil Trav. Chim. Pays-Bas 1978, 97, 286.

^{89.} Allinger, N.L.; Freiberg, L.A. J. Am. Chem. Soc. 1960, 82, 2393.

greater, making the transannular interaction much higher in energy relative to the hydrogenhydrogen interaction of cyclohexane. *This is* $A^{1,3}$ *strain.* In 1,3-dimethylcyclohexane (**198**) and in 1,3,5-trimethylcyclohexane (**199**) $A^{1,3}$ -strain increases significantly as the steric interactions increase. This $A^{1,3}$ -strain destabilizes the conformations with the axial substituents, shifting the equilibrium to the lower energy chair form that has the substituents in the equatorial position. Returning to **196B**, it is clear that each axial *tert*-butyl group will interact with the two axial hydrogen atoms on its side of the ring, leading to significant $A^{1,3}$ -strain) estimated to be about 12 kcal mol⁻¹ (50.2 kJ mol⁻¹) or 6 kcal/*tert*-butyl group.⁹⁰ There is no question that the equilibrium for the two chair conformations will shift to favor the chair with the two *tert*-butyl groups in the equatorial position, effectively eliminating the $A^{1,3}$ -strain.



Figure 1.14. A^{1,3} Strain in Cyclohexane, Methylcyclohexanes.

Closer inspection of **196C** reveals that $A^{1,3}$ -strain has been eliminated but the 1,2-diequatorial *tert*-butyl groups are in close proximity, producing a new type of strain called *G* strain. The energy of the interaction (the *G* value)⁹¹ is 2.5 kcal mol⁻¹ (10.47 kJ mol⁻¹), per *tert*-butyl group (see Fig. 1.15). This type of steric interaction is analogous to the interactions found in the *gauche* butane conformation, and is often referred to as a *gauche* interaction. If we take cyclohexane as a model the trans-diequatorial hydrogens in **172**E show little interaction, but replacing them with methyl (see *trans*-1,2-dimethylcyclohexane, **200**) causes significant *G*-strain. When the two *tert*-butyl groups in **196** are trans-diequatorial (see **196C**), the interaction is very large and destabilizes that conformation. If both chair conformations have high energy interactions, the molecule will distort to minimizes these interaction, and **196** exists largely in either the boat or the twist-boat.

^{90.} Winstein, S.; Holness, N.J. J. Am. Chem. Soc. 1955, 77, 5562.

^{91.} Corey, E.J.; Feiner, N.F. J. Org. Chem. 1980, 45, 765.



Figure 1.15. G Strain in 1,2-Dimethylcyclohexane and 1,2-Di-tert-butylcyclohexane.

Why are these physical chemistry concepts being discussed in a reactions-synthesis book? It will be apparent throughout this book that the conformation of a molecule has a critical effect on the reactivity and stereochemistry of many reactions. Strain energies that influence the conformation of a molecule can be quantified in some cases, and the percentage of each conformation can be calculated. With such information we can make more reasonable predictions of reactivity and stereochemistry. The following protocols are presented in an attempt to reinforce the idea that conformational analysis is a critical part of synthetic analysis, and to introduce the most basic approaches to conformational analysis.

We will focus on cyclohexane derivatives to illustrate the fundamental idea. When a reagent approaches a cyclohexane ring, the conformation of the ring will influence how the reagent interacts with any functional group on that ring. The populations of the two chair conformations can influence the relative rate and the stereochemical outcome of a given reaction. The relative populations of both chair conformations in cyclohexane derivatives can be predicted with some accuracy by calculating the *A* and/or *G* values. For a monosubstituted cyclohexane, two chair forms are possible (**201** and **202**) and they are in a dynamic equilibrium. If $X \neq H$, the diaxial steric interaction (*A* strain) in **201** will be larger than in **202** and a higher percentage of **202** is expected. This non-bonded interaction can be measured in terms of F° , the conformational free



energy.⁹² Since there are two conformations of differing energies, this difference is represented by (ΔF°) ,^{86a} and it is possible to relate this energy term to the free energy of the system by: $\Delta G^{\circ} = \Delta H^{\circ} - T\Delta S^{\circ}$. For a given temperature, the entropy term will be small relative to ΔF° (taken to be ΔH° hereafter) and a second assumption can be made, that $\Delta S^{\circ} = 0$, leading to $\Delta G^{\circ} \approx \Delta H^{\circ}$.

The ΔS° term is not zero, but is usually measured in calories (J) and the ΔH° term in kilocalories (KJ), so ignoring ΔS° will introduce only a small error into the calculation. Lowry and

^{92. (}a) Eliel, E.L. J. Chem. Educ. 1960, 37, 126; (b) Reference 12, pp 694-698; (c) Reference 31b, pp 234-239; (d) Reference 86a, pp 138-140; (e) Hammett, L.P. J. Am. Chem. Soc. 1937, 59, 96; (f) Hammett, L.P. Physical Organic Chemistry, 2nd Ed., McGraw-Hill, New York, 1970, p 347ff; (g) Jaffé, H.H. Chem. Rev. 1953, 53, 191; (h) Hansch, C.; Leo, A.J. Substituent Constants for Correlation Analysis in Chemistry and Biology, Wiley, New York, 1979; (i) Reference 12, p 654.

Richardson's⁹³ list of ΔH° and S°_{298} values for a variety of specific bonds demonstrates this difference. In the C- Me bond, for example, ΔH° is -10.08 kcal mol⁻¹ (42.2 kJ mol⁻¹) and S°_{298} is 30.4 cal mol⁻¹ (127.2 J mol⁻¹). Similarly, ΔH° for cyclopropane is listed as 27.6 kcal mol⁻¹ (115.5 kJ mol⁻¹) and S°_{298} is 32.1 cal mol⁻¹ (134.3 J mol⁻¹).⁹³

The ΔH° term is related to ΔG° , the free energy, which is related to the equilibrium constant by the expression: $\Delta G^{\circ} = -2.303$ RT log K_{eq}. The conformational equilibrium between **201** and **202** is represented by K_{eq} , which can be calculated from the percentage of the two conformers: $K_{eq} = \% 202 / \% 201$, where % 201 + % 202 = 100%. Note that a general discussion of the Curtin-Hammett principle^{92c-f} (product composition is related to the relative concentrations of the conformers)⁹²ⁱ may be of value in any discussion of this equilibrium reaction.

For this process to work, some estimation of F° (hereafter called H°) must be made. In connection with the development of the interactive synthesis computer program *L*ogic and *H*euristics *A*pplied to *Synthetic Analysis* (LHASA, sec. 10.4.B),^{1,5} Corey developed a protocol for determining the conformational energies of cyclohexane derivatives,⁹¹ and assembled a list of *H* values for various substituent interactions in Table 1.4.⁹¹ This table is related to a similar one, first assembled by Hirsch and co-workers.^{94,95} The energy for a given conformation is taken to be the sums of all monoaxial interactions (*A* values), any 1,2-diequatorial interactions (*G* values) and any multiple diaxial interactions (defined by Corey as *U* values⁸⁶ and found in the two structures labeled). Simple doubling or tripling of the appropriate *A* value did not give correct results in this latter case and more accurate *U*-values were required. Note that the *A* and *U* values are identical in many cases. They usually differ if the substituent contains unsaturation.

The protocol for calculating the percentage of each conformation is illustrated by the two chair conformations of 2-chloro-3,4-dimethylcyclohexanol, **203** and **204**. Using Table 1.4, the pertinent interactions are U_{OR} , the two $U_{\text{CH}_{2\text{R}}}$ and U_{Cl} in **203** and the two $G_{\text{CH}_{2\text{R}}}$, G_{OR} and G_{Cl} in **204**.



$$\Delta H^{\circ} = H_{\text{product}} - H_{\text{reactant}} = H_{204} - H_{203} = (G_{\text{CH}_2\text{R}} + G_{\text{C1}} + G_{\text{CH}_2\text{R}} + G_{\text{OR}}) - (U_{\text{OR}} + U_{\text{CH}_2\text{R}} + U_{\text{CH}_2\text{R}} + U_{\text{C1}}) = (0.4 + 0.5 + 0.4 + 0.2) - (0.8 + 1.8 + 1.8 + 0.4) = (1.5) - (4.8) = -3.3 \text{ kcal mol}^{-1} (-13.8 \text{ kJ mol}^{-1}).$$

^{93.} Reference 86a, pp 164-165.

^{94.} Hirsch, J.A. in *Topics in Stereochemistry, Vol. 1*, Allinger, N.L.; Eliel, E.L. (Eds.), Wiley-Interscience, New York, *1967*, pp 199-222.

^{95. (}a) Reference 31b, pp 236-237; (b) Barrett, J.W.; Linstead, R.P. J. Chem. Soc. 1936, 611. For a list of energy values for several functional groups, see Reference 12, pp 696-697.

	$ \begin{array}{c} X \\ H \\ H \\ A \\ G \end{array} $	X H or X Y U U	X ¹
Group	A (kcal mol ⁻¹) ^a	G (kcal mol ⁻¹) ^a	$U (\mathrm{kcal} \mathrm{mol}^{-1})^{\mathrm{a}}$
н	0	0	0
F	0.2 (0.84)	0	0
Cl	0.4 (1.67)	0.5 (2.09)	0.4 (1.67)
Br	0.4 (1.67)	0.8 (3.35)	0.4 (1.67)
I	0.4 (1.67)	1.0 (4.19)	0.4 (1.67)
PR ₃	1.6 (6.7)	1.6 (6.7)	1.6 (6.7)
SR	0.8 (3.35)	0.5 (2.09)	0.8 (3.35)
S(O)R	1.9 (7.95)	2.7 (11.30)	1.9 (7.95)
S(O ₂)R	2.5 (10.47)	3.5 (14.65)	2.5 (10.47)
OR	0.8 (3.35)	0.2 (0.84)	0.8 (3.35)
NH_3^+	2.0 (8.37)	0.5 (2.09)	2.0 (8.37)
NR_3^+	2.1 (8.79)	0.5 (2.09)	2.1 (8.79)
NHR	1.3 (5.44)	0.3 (1.26)	1.3 (5.44)
N=	0.5 (2.09)	0.1 (0.42)	0.5 (2.09)
N≡	0.2 (0.84)	0.1 (0.42)	1.2 (5.02)
NO_2	1.1 (4.61)	0.3 (1.26)	0.5 (2.09)
C≡	0.2 (0.84)	0	1.2 (5.02)
aryl	3.0 (12.56)	1.2 (5.02)	0.5 (2.09)
CO_2^-	2.0 (8.37)	0.5 (2.09)	2.0 (8.37)
CHO	0.8 (3.35)	0.3 (1.26)	0.8 (3.35)
C=	1.3 (5.44)	0.2 (0.84)	0.9 (3.77)
CR ₃	6.0 (25.11)	2.5 (10.47)	6.0 (25.11)
CHR ₂	2.1 (8.79)	0.8 (3.35)	2.1 (8.79)
CH ₂ R	1.8 (7.54)	0.4 91.67)	1.8 (7.54)
^a The value in parentheses is the energy in kJ mol ⁻¹			
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Table 1.4. Corey's A, G, and U Values for Calculating Conformational Energies of Cyclohexane Derivatives.

If $\Delta H^{\circ} \approx \Delta G^{\circ}$, then assume $\Delta G^{\circ} = -3.3 = -2.303 \ RT \log K_{eq}$. At 25°C, -2.303 RT = -1.364. Therefore,

 $\Delta G^{\circ} = -3.3 = -1.364 \log K_{eq}$ sp log $K_{eq} = -3.3/-1.364 = 2.42$ and $K_{eq} = 10^{2.42} = 262.6$.

Since %203 + %204 = 100%, where 204 = 1 - 203, then $K_{eq} = 204/203 = 1-204/203$ and K_{eq} (203) = 1 - 203);

so, 262.6(203) = 1 - (203), and 262.6(203) + (203) = 1 or 262.6 + 1(203) = 1, which leads to

(203) (263.6) = 1 and (203) = 1263.6 = 0.0038

Therefore, there is 0.38% of **203** and 99.62% of **204**. *Remember that two major assumptions* were made for this calculation: (1) all conformations except **203** and **204** were ignored, and (2) ΔS° was assumed to be zero.

As first shown by Barton,⁸⁷ the relative percentage of a given conformation directly influences the rate of a reaction. As summarized by Eliel,^{92a} the equilibrium between **205** and **206** is given by the equilibrium constant (*K*), and the rate of conversion of each conformation to product is given by k_{205} and k_{206} , as developed by Winstein and Eliel.^{92a} The overall rate will be Rate = k [C], where k is the observed specific rate and [C] is the stoichiometric concentration of the cyclohexane.^{92a} Rate = $k_{205} [205] + k_{206} [206]$ for this system, and the value k is related to the equilibrium constant as shown in the following:



As mentioned above, the percentage of a given conformation is an essential factor in determining the rate and viability of a given reaction and these calculations allow the synthetic chemist to estimate conformational populations. Just as the minor chair conformation influences the rate, so other conformations (boat, twist-boat, etc.) can also exert an influence, depending on their relative populations.

MOLECULAR MODELING: Conformers of Cyclohexane

It is well known that cyclohexane adopts a chair conformation. Actually, the molecule exists in both chair and twist-boat conformers. The chair structure is the lower-energy conformer (quantum chemical calculations suggest that the twist-boat conformer is \sim 30 kJ/mol higher in energy), and the two interconvert via a low-energy half-chair transition state. The large energy difference and the small barrier to interconversion mean that detecting (let alone isolating) twist-boat cyclohexane is nearly impossible. Quantum chemical calculations show that a temperature in excess of 1500 K would be needed to achieve 10% of an equilibrium mixture of these conformers.

Interconversion of equivalent chair conformers of cyclohexane may be thought of as proceeding in two stages that "mirror" each other. The first is interconversion of one chair conformer to the twist-boat conformer via a half-chair transition state, and the second is interconversion of the twistboat conformer to the second chair conformer via a second (equivalent) half-chair transition state. A plot of the energy profile for the process appears on screen. You can step through the individual structures that make up the sequence or "animate" it using the **Step** and **Play** keys, respectively at the bottom left of the screen.

MOLECULAR MODELING: Conformers of Cyclohexane, con't

Substitution should change the relative energies of chair and twist-boat conformers of cyclohexane. First, build and obtain energies for both chair and twist-boat conformers of cyclohexane. For each in turn, *click* on > to the right of the tab(s) at the top of the screen and select *Continue*. The chair structure can be taken from the **Rings** menu. Build the twist-boat conformer by joining the ends of a chain of sp³ carbons into a distorted boat-like structure. Next, build both chair and twist-boat conformers for the *cis* isomers of 1-2-dimethylcyclohexane, 1,2-di-*tert*-butylcyclohexane and 1-2-diphenylcyclohexane and obtain energies for each. Use the same sequence of operations (*click* on > and select *Continue*) as before in order to keep the text on screen. Is the chair-twistboat energy difference for any of these disubstituted molecules significantly less than that for cyclohexane itself?

In addition to the values in Table 1.4 used for calculations of substituted cyclohexane derivatives,⁸⁵ Corey developed formulas for several other cyclic molecules. Incorporation of two halogens with a 1,2- or 1,4-diaxial relationship on a cyclohexane ring led to a higher proportion of the diaxial conformer⁹⁶ due to the more favorable electrostatic interactions of the lone pair electrons.⁹⁷ Corey's models in this case were **207** and **208**, and the equation used to calculate the conformational energy is $E = 1/2 (A_x + A_y)$. Introduction of a π -bond or a heteroatom in the cyclohexane ring changes the energy relationships, since the presence of a π bond flattened the ring. The usual U and G values were used for monosubstituted or disubstituted derivatives such as **209** or **210**, respectively. A carbonyl or an aldehyde unit led to a diminished value for A, and a spirocyclic or fused ring structure also diminished A. Introduction of an oxygen in the ring (to form a pyran) led to a diminished value for A.



Corey and co-workers⁹¹ also developed parameters to evaluate boat conformations, which are often important contributors to the conformational population of cyclohexane derivatives (see above). The energies for boat conformations with one or more substituents in the flagpole

^{96.} Jensen, F.R.; Bushweller, C.H. Adv. Alicyclic Chem. 1971, 3, 139.

^{97.} Wood, G.; Woo, E.P.; Miskow, M.H. Can. J. Chem. 1969, 47, 429.

positions use a new term (*b*): $E = (b^1 + b^2) A^R$ for **211**, and $E = (b^1 + b^2) (U^R + U^{R'})$ for **212**), derived from the bowsprit-flagpole interactions (R-H in **211** or R¹-R in **212**). Introduction of a π bond, a cyclopropane or a cyclobutane ring flattens the boat, leading to increased destabilization. Fused five-membered rings and larger fused rings do not flatten the ring of interest.



These structural types emphasize that the presence of π bonds and heteroatoms will influence the overall conformation. "Flattening" of a ring is often an important structural feature of natural products and other attractive synthetic targets. The π bond in a cyclohexene moiety flattens the ring in **213A** and its other low-energy conformer, **213B**. These are actually halfchair conformations analogous to **177**.⁹⁸ The isopropyl group (*i*-Pr) is less stable in the pseudoaxial position and more stable in the pseudo-equatorial position.⁹⁹ The *i*-Pr \Leftrightarrow Br interaction is largely alleviated in **213B**. This effect is compatible with **213B** as the major conformation and higher relative energy for **213A**.

MOLECULAR MODELING: Axial/Equatorial Preferences in Disubstituted Cyclohexanes

It is well known that substituents on cyclohexane generally (but not always) prefer to be *equatorial*. Where there are two different substituents and only one can be *equatorial*, for example, in a *cis*-1,4-disubstituted cyclohexane, the substituents will "compete" for the favored position. Build the conformer of cis-1-bromo-4-*tert*-butylcyclohexane with the Br *axial* and the *tert*-butyl group *equatorial* and obtain its energy. Next, *click* on > to the right of the tab at the top of the screen and select *Continue* to bring up a fresh builder palette. Build the conformer in which the Br is *equatorial* and the *tert*-butyl group is *axial* and determine its energy. Which substituent, bromine or *tert*-butyl, "wins" the competition and assumes the *equatorial* position? Is the higher energy conformer likely to be observed in a room-temperature equilibrium distribution? Hint: a 95:5 ratio of major to minor conformers corresponds to an energy difference of around 8 kJ/mol.

A similar competition exists for disubstituted cyclohexenes, for example for cis-3-bromo-6-*tert*butyl-1-cyclohexene. Obtain energies for the two possible conformers (bromine *axial* and *tert*butyl *equatorial* and *vice versa*). Which substituent, bromine or *tert*-butyl, assumes the *equatorial* position? Is the difference in energy between the conformers, smaller, larger or about the same as for *cis*-1-bromo-4-*tert*-butylcyclohexane? If smaller or larger, examine the geometries of the two cyclohexane conformers and two cyclohexene conformers to provide an explanation.

^{98. (}a) Böeseken, J.; de Rijck van der Gracht, W.J.F. Rec. Trav. Chim. 1937, 56, 1203; (b) Reference 31b, p 239.

^{99. (}a) Reference 31b, p 240; (b) Dauben, W.G.; Pitzer, K.S. in *Conformational Analysis in Steric Effects in Organic Chemistry*, Newman, M.S. (Ed.), Wiley, New York, **1956**, pp 38-39.

Similar conformational effects arise in other functionalized systems, including reactive intermediates. Conversion of cyclohexanone to its enolate anion (214A, see sec. 9.2) flattens the ring (see 214B), and leads to a cyclohexene-like conformation. Note the conformational similarity of 214A to cyclohexene derivative 213A. The dimethylamino enamine (see sec. 9.6) of cyclohexanone (215A) also shows this half-chair conformation (see 215B). In these cases, the lone pair electrons (on oxygen in 214 and on nitrogen in 215) overlap with the π bond.



When compared to chair cyclohexane, the presence of the trigonal planar carbonyl in cyclohexanone removes the 1,3-diaxial hydrogen atom interactions and, as seen in the models for Corey's calculations, partially flattens the ring. The conversion of alcohol **216** to ketone **217** illustrates this point. Although **216** is an equilibrating mixture with an axial or equatorial hydroxyl group, upon oxidation to the ketone the flattening effect of the carbonyl is easy to see. Energetically, the R \leftrightarrow OH interaction (U value) in **216** is removed upon oxidation to **217**. In the ketone, the carbonyl effectively eclipses the α -equatorial hydrogens, further lowering the conformational energy.¹⁰⁰ Ketone **217** exists as an equilibrating conformational mixture favoring the R group in an equatorial position.

Exocyclic methylene compounds such as **218** will exhibit the same flattening effect observed with the carbonyl group. An interesting effect is seen in the conversion of **218** to **219** or **220**, where *A* strain is increased in the products, relative to the methylene group. Further, the greater *A* strain of methyl (1.8 kcal mol⁻¹ in Table 1.4) versus 0.4 kcal mol⁻¹ for Br (7.5 and 1.7 kJ mol⁻¹ respectively) suggests that **219** may predominate after addition of HBr to the alkene (see sec. 2.10.A). This analysis ignores the relative trajectories of approach of the reagents (see sec. 6.6.A) and other steric interactions, however.

^{100. (}a) Allinger, N.L.; Blatter, H.M. J. Am. Chem. Soc. 1961, 83, 994; (b) Allinger, N.L.; Freiberg, L.A. Ibid 1962, 84, 2201.



MOLECULAR MODELING: Electrophilic Bromination of Methylenecyclohexane

Electrophilic bromination of 4-*tert*-butylmethylenecyclohexane can lead to either **219** or **220**. The mechanism presumably involves addition of "H⁺" to the external methylene carbon, follow by attack of Br⁻ on the resulting carbocation. Examine a LUMO map for the intermediate carbocation. This colors an electron density surface depicting the overall molecular size and shape with the value of the lowest-unoccupied molecular orbital. By convention, regions on the surface where the LUMO is concentrated are colored "blue" while those where it is absent are colored "red". Bromide would be expected to add where the LUMO is most concentrated. Is there a clear preference for addition to one face of the carbocation over the other? If there is, which product would be favored, **219** or **220**?

In addition to the endocyclic double bond usually found in an enolate anion such as **214**, enolate anions can be formed that have an exocyclic double bond (also see sec. 9.5.D). Relief of strain will presumably assist formation of the enolate anion, and may influence the final stereochemistry of groups in the product when the enolate anion reacts with an a suitable reagent (see sec. 9.3.A, 9.4).¹⁰¹ This effect can also be seen in the equilibration of the cis-ester **221** to the trans-ester **223** via the planar enolate (**221**).⁹⁸ This equilibration (accomplished by treating **221** with a base followed by a proton source) favors **223** due to reduction of the *A* strain of the axial carboethoxy group in $[A_{COOR} = 1.20 \text{ kcal mol}^{-1} (4.99 \text{ kJ mol}^{-1})].$

Six-membered rings containing oxygen (pyran derivatives based on **224**) are an integral part of carbohydrates such as α -D-glucopyranose (**225**). Less substituted pyrans show similar effects. The presence of the α -alkoxy group in **229** leads to a significant effect also seen in α -alkoxy pyrans, the **anomeric effect**.¹⁰² An alkyl group on cyclohexane or pyran usually prefers the equatorial position due to increased *A* strain. When an alkoxy group is attached to pyran, however, it prefers the axial position. This effect is probably due to dipolar interactions of the oxygen lone pairs (see **226A** and **226B**).¹⁰³ The anomeric effect is evident in glucose, where α -D-glucopyranose (**225**) accounts for a significant portion of the conformational equilibrium.

^{101.} Reference 52a, p 67.

⁽a) Lemieux, R.U. Pure Appl. Chem. 1971, 27, 527; (b) Angyal, S.J. Angew. Chem. Int. Ed. 1969, 8, 157;
(c) Kirby, A.J. The Anomeric Effect and Related Stereoelectronic Effects at Oxygen, Springer-Verlag, New York, 1983.

^{103.} David, S.; Eisenstein, O.; Salem, L.; Hehre, W.J.; Hoffmann, R. J. Am. Chem. Soc. 1973, 95, 3806.



The influence of substituents on conformational stability is also evident in amines such as *N*-ethyl piperidine. The chair conformation can be drawn with the ethyl group axial (N lone pair equatorial in **227A**) or equatorial (N lone pair axial as in **227B**). The greater *A* value for ethyl than for the lone pair suggests a predominance of **227B** in this equilibrium mixture. This preference for the larger group being in an equatorial position is analogous to the effects seen in pyrans and cyclohexanes.



MOLECULAR MODELING: Conformational Mobility of Tetrahydropyran Rings

Compounds **A-D** were isolated from *Aplysia kurodai* by Kakisawa and co-workers (*J. Org. Chem.* **1987**, 52, 4597-4600). Proton NMR was used to assign the structures of **C** and **D**, but led to ambiguous results for **A** and **B**. (An X-ray crystal structure was required to verify the structure of **B**, which was then used to elucidate the structure of **A**). The authors interpreted the NMR results to indicate that **A** and **B** are conformationally mobile whereas **C** and **D** are rigid.



While rotation about single bonds is normally too rapid to be "frozen out" in an NMR experiment, chair-chair interconversion in cyclohexane (and presumably tetrahydropyran) derivatives is much slower and can be stopped at low temperatures. One after the other, build and obtain the energy for the two different chair conformers or either **A** or **B** (or both) and of **C** or **D** (or both). Note that you need to consider the possible conformations about the bond connecting the ring to the vinyl group, choosing the lowest energy for each. Hint: Try the vinyl group "up" and the vinyl group "down" to begin, determine the energy of each and then try one or two other vinyl conformations. For the second and following calculations, *click* on > to the right of the tab at the top of the screen and select *Continue* to bring up a fresh builder palette. Are the energies of the two chairs for **A** (or **B**) similar or significantly different? Are the energies of the two chairs for **C** (or **D**) similar or significantly different? If (**A** (or **B**) and **C** (or **D**) exhibit different behavior, suggest why. Are your results in line with the conclusion from the NMR experiments, that **A** and **B** are conformationally mobile while **C** and **D** are not?

The presence of bulky substituents, or substituents capable of chelation or hydrogen bonding can alter conformational populations,^{104,105} as first seen with ethylene glycol. In **228A**, there are two effects that influence the conformation.¹⁰⁶ Bulky substituents lead to large A and G strain in both chair conformations. In addition, internal hydrogen bonding of the glutarimide moieties helps stabilize the twist-boat conformation shown in **228B**, which is the lowest energy conformation of this molecule. The 3D model shows the twist in the cyclohexane moiety as well as the proximity of the two diketopiperazine units. The twist-boat conformation is also observed in the absence of internal hydrogen bonding. As confirmed by X-ray crystallography, *cis,trans,trans*-1,2,4,4-tetraisopropylcyclohexane exists as a twist-boat.¹⁰⁷



As mentioned in an earlier example, the reduction of cyclooctanone (186) shows how conformations can influence reactivity. Treatment of 186 with lithium aluminum hydride (LiAlH₄, see sec. 4.2.B) generates the alcohol (185). The alcohol will have greater transannular strain than the ketone. The reduction may be somewhat sluggish relative to similar reduction of cyclohexanone. The oxidation, however, converts 185 to 186 using chromium trioxide (see sec. 3.2.A) and leads to diminished strain as the newly introduced carbonyl flattens the ring slightly. As the product is somewhat more stable than the starting material, the oxidation is more facile. Similarly, formation of the enolate (186 \rightarrow 229) with lithium diisopropylamide (LDA, see sec. 9.2.B) should be facile due to relief of transannular strain for formation of the planar enolate moiety. A subsequent alkylation step (229 \rightarrow 230, see sec. 9.3.A) may be sluggish, however, since the methyl group in 230 may introduce a bit more strain in the product (remember there are several other low energy conformations for the eight-membered ring) than in the original unsubstituted cyclooctanone (186).



^{104.} Reference 18, p 200.

- 105. (a) Stolow, R.D. J. Am. Chem. Soc. 1961, 83, 2592; (b) Stolow, R.D.; McDonagh, P.M.; Bonaventura, M.M. Ibid 1964, 86, 2165.
- 106. Witiak, D.T.; Wei, Y. J. Org. Chem. 1991, 56, 5408.
- 107. Columbus, I.; Cohen, S.; Biali, S.E. J. Am. Chem. Soc. 1994, 116, 10306.

MOLECULAR MODELING: Thermodynamic Control of Product Distributions

Where reactions have very low energy transition states, thermodynamics is likely to control product distribution. Reactions that involve protonation followed by deprotonation are good examples. In the gas phase and in non-interacting solvents, both protonation and deprotonation occur with little or no barrier, meaning that final product distributions are dictated only by relative product energies. In the presence of aqueous acid, the hydroxy acid shown below does not give rise to its lactone (lactone A) but rather to lactone B. This reaction occurs via protonation of the hydroxyl unit of the acid, followed by displacement of the hydronium ion by the carboxyl unit. The carbon in lactone B proximal to the lactone oxygen atom has undergone epimerization from (S) to (R). This transformation requires that the initially formed oxonium ion is displaced by water, with inversion, to form a new oxonium ion, and subsequent reaction with the carboxyl group leads to lactone-B. Why should the epimerization reaction be preferred to direct lactone formation?



Assuming that the reaction is under thermodynamic control, the lactone that is formed will be the more stable lactone, irrespective of how it was formed. Build lactone-A and obtain its energy. *Click* on > to the right of the tab at the top of the screen and select *Continue* to bring up a fresh builder palette. Build lactone-B and obtain the energy. Which lactone is lower in energy? Suggest a reason for this preference. Does the information you have obtained suggest a reason for the observation that epimerization followed by formation of-B occurs preferentially to direct formation of lactone-A? Elaborate.

1.5.D. Conformations in Polycyclic Molecules



The conformational constraints in monocyclic molecules are magnified in bi-, tri-, and polycyclic molecules. A simple case is cyclohexene oxide (231) where the planar three-membered ring flattens the ring. Similar effects are seen in cyclohexene, and also occur when cyclopropane is

fused to a ring. Bicyclo[3.1.0]hexanes also show this flattening effect. An example is carane (232), which exists primarily in the conformation shown (note that the geminal dimethyl groups are perpendicular to the plane of the cyclopropane ring). The cis-isomer (233) is expected to show a significant Me-Me interaction, which is not present in the trans-isomer, 232 (carane).

The conformational constraints peculiar to [m.n.0]alkanes (n \neq 1) can be illustrated by comparing the cis- and trans- isomers of bicyclo[3.3.0]octane (234), hydrindane (235), as well as 236 (decalin). Each five- and six-membered ring tends to assume an envelope conformation or a chair conformation respectively in their lowest energy form. *cis*-Bicyclo[3.3.0]octane (237) shows a bent conformation with the two envelope shapes relieving some of the cross ring interactions.^{108,92} *trans*-Bicyclo[3.3.0]octane (238) shows a more extended or open structure, and there is some distortion of the five-membered ring. Compound 238 is ~ 6 kcal mol⁻¹ (25.1 kJ mol⁻¹) higher in energy than 237.¹⁰⁹ Both cis- and trans- isomers are easily prepared, however.¹¹⁰



Hydrindanes have the five-membered ring in the envelope conformation with the six-membered ring in a chair. The *cis*-indane (**239**) shows a 1,3-diaxial interaction with substituents, and there is a *gauche*-like interaction. In the trans-isomer (**240**), the 1,3-diaxial interaction is diminished, and the extended conformation in **240** is slightly lower in energy (about 1 kcal mol⁻¹ or 4.19 kJ mol⁻¹) than **239**.¹¹¹ Similar analysis of *cis*-decalin (**241**) and *trans*-decalin (**242**) leads to the same bent and extended forms, with both six-membered rings in a chair conformation.¹¹² In **241**, one ring can assume more of a boat like structure in some conformations. There is a 1,3-diaxial interaction in substituted **241**, and the overall energy of **241** is lower due to decreased nonbonded interactions.¹¹³ Eliel describes the conformations of several other bicyclic and polycyclic compounds.¹¹⁴

- 113. (a) Reference 31b, p 279; (b) Hückel, W. Annalen, 1925, 441, 1; (c) Hückel, W.; Friedrich, H. Ibid 1926, 451, 132.
- 114. Reference 12, pp 780-793.

^{108.} See reference 12, p 776.

^{109. (}a) Reference 12, pp 774-775; (b) Reference 31b, p 274.

^{110.} Owen, L.N.; Peto, A.G. J. Chem. Soc, 1955, 2383.

 ⁽a) Reference 12, pp 776-779; (b) Reference 31b,p275; (c) Browne, C.C.; Rossini, F.D. J. Phys. Chem. 1960, 64, 927.

^{112.} Turner, R.B. J. Am. Chem. Soc. 1954, 74, 2118.



Incorporation of a π bond from an alkene or aryl moiety into a bicyclic system leads to significant flattening of the ring. Examples are **243A** (9-decalene) and the benzene-containing derivatives tetrahydronaphthalene (**244A**) and 1*H*-dihydroindene (**245A**). The planar alkene moiety in **243A** (see **243B**) forces the four allylic carbons to be coplanar and each ring more or less behaves as if it were cyclohexene. The planar benzene ring in **244A** (see **244B**) imposes similar conformational constraints, and the carbons of the nonaromatic ring assume a conformation similar to cyclohexene. In **245A** (see **245B**), the nonplanar cyclopentane ring behaves more or less like cyclopentene. The presence of three or more fused rings is rather common in nature. The natural product hirsutene (**246A**)¹¹⁵ also shows the conformational bias imposed by three fused five-membered rings (see model **246B**).



115. For leading references relating to the structure and synthesis of this molecule, see (a) Hua, D.H.; Venkataraman, S.; Ostrander, R.A.; Sinai, G.-Z.; McCann, P.J.; Coulter, M.J.; Xu, M.R. J. Org. Chem. 1988, 53, 507; (b) Curran, D.P.; Raciewicz, D.M. Tetrahedron 1985, 41, 3943.



A last example of this phenomenon is seen in the steroid nucleus (247A). Each of the cyclohexane moieties will exist in a chair conformation and the cyclopentane will be in an envelope conformation, as seen in 247B. If a carbonyl or alkene moiety is included, the six-membered ring will be flattened and its conformation will be very similar to that of cyclohexane or cyclohexene. As seen in conformational drawing 247B, each trans-fused cyclohexane ring resembles *trans*-decalin and the four fused rings impart great conformational rigidity to the molecule. Only the terminal cyclohexyl and cyclopentyl rings have some mobility. The interaction R¹-R²-Me of the cyclohexane ring is important, as are the R³-Me and R-R⁴ interaction of the cyclopentane ring. Examples of the conformational variations in steroids are seen by examination of cholesterol (248A) and β -estradiol (249A).¹¹⁶ When the A ring is aromatic, as in estradiol (249), the A/B ring system is flattened, inducing significant distortion in the C ring as well (see 249B relative to 248B). Changes in conformation for polycyclic systems can often be predicted using the simple five- and six-ring models discussed above.



It is reasonable to assume that the simple concepts introduced for monocyclic rings such as cyclopentane, cyclohexane, cyclohexene, and cyclohexanone can be applied with little change to complex molecules containing those units. Throughout this book the analysis of simple rings will be used to understand the conformational bias and reactivity of larger and more difficult synthetic targets.

^{116.} Fieser, L.F.; Fieser, M. Steroids, Van Nostrand Reinhold, New York, 1959.

1.6. CONCLUSION

This chapter has reviewed the most fundamental concepts of stereochemistry and conformational analysis, with some applications to more complex problems. For students who have had a good undergraduate Organic chemistry course, it is intended as a review since these concepts are integral to the understanding of organic reactions. The concept of disconnection and retrosynthetic analysis is a prelude to a discussion of synthetic strategies in Chapter 10. The disconnection method and pertinent transforms will, however, be presented in virtually every chapter as new reactions are introduced.

The introduction to organic reactions will be continued in the functional group exchange reactions in Chapter 2, which will review the reactions introduced in a typical first Organic chemistry course. Some of the concepts will be expanded and updated to include more synthetically useful reactions. Oxidation and reduction will be presented in separate chapters to focus attention on the vast number of reactions that fall under these categories.

HOMEWORK

 For each of the following molecules calculate the percentage for both chair conformations using the values in Table 1.4. Calculate using the temperatures 150°C for (a), 35°C for (c) and 25°C for (b) and (c).



2. Determine the absolute configuration (*R* or *S*) for every stereogenic center in the following molecules:



3. Determine the absolute configuration for every stereogenic center in the following molecules:



- 4. For disconnect fragments **23** and **24** in Section 1.2, convert each to a real molecule using synthetic equivalents in Table 1.2. Briefly discuss the retrosynthetic and synthetic sequences and show the complete retrosynthetic analysis based on this disconnection.
- 5. Using the reaction wheel (Fig. 1.1) give reasonable syntheses, including reagents and all intermediates (no mechanisms).



- 6. Use the *Compendium of Organic Synthetic Methods* (Vol. 11) to give three *different* reactions (with literature references and reactions) for each of the following:
 - (a) acids from nitriles
 - (c) amides from halides
 - (e) ethers from halides
 - (g) ketones from olefins
- (b) aldehydes from nitriles
- (d) amines from nitriles
- (f) halides from amines
- (h) alkenes from aldehydes
- 7. Draw molecule **A** in what should be the low-energy conformation. Briefly discuss the conformation for the highlighted rings in molecule **A**. Also discuss the conformational preference (axial or equatorial) for all both methyl groups as well as the hydroxyl.



8. Use a 3D computer drawing program, draw molecules (a) and (b) in 3D form, from the indicated perspective (see the example below).



9. Determine the absolute configuration (R or S) for each chiral axis in the following molecules:



10. Determine the absolute configuration for each chiral center in the following molecules.:



11. The conversion of the hydroxy-acid shown to the right, to the corresponding lactone, is rather slow. When pushed under aqueous acid conditions, epimerization at the carbon bearing the hydroxyl can occur. Draw the lactone and explain the observations noted in this question. $\frac{H_{H_{e}}}{H_{OH}} = \frac{1}{H_{e}} = \frac{1}{H$

- 12. Explain why *cis*-1,3-cyclohexanediol exists mainly in the diaxial conformation in aqueous ethanol solution, when by Corey's ΔG calculations (see Table 1.4), the diequatorial conformation should be lower in energy.
- 13. Determine the correct *re/si* label for each prochiral atom in the following molecules.



14. Draw the three most significant anti-rotamers of 1-phenyl-1-ethanol (R = Me in the accompanying diagram), and correlate them with the rotamers marked a-c on the energy curve.



15. (a) Draw the (2*S*, 3*R*,4*R*) and the (2*S*, 3*S*, 4*S*) derivative of molecule **A**. (b) Draw both the erythro/threo and the syn/anti forms of molecule **B**.



16. Classify each of the following reactions as stereospecific/stereoselective and/or regiospecific/regioselective.



- 17. Explain why the ground state energy of cyclodecane is higher than that of cyclooctadecane. Why is cyclopentadecane higher in energy than cyclohexadecane?
- 18. Draw the boat conformation of *cis-,trans-,trans-*1,2,3,4-tetraisopropylcyclohexane.

Acids, Bases and Functional Group Exchange Reactions

2.1. INTRODUCTION

chapter

In most syntheses, the main focus is usually on construction of the molecule using carboncarbon bond forming reactions. Most of the actual chemical reactions in a synthesis, however, are those that incorporate or change functional groups. Such reactions are known as functional group exchange reactions, and this chapter will review major reaction types involved in functional group exchanges. For all practical purposes, this discussion also constitutes a review of a typical undergraduate organic course.

Figure 1.1 showed that many functional group interchange reactions are chemically related. These transformations usually proceed via ionic intermediates and/or polarized C-X bonds, or they involve π bonds. A short list of typical reagents was provided in that Figure, but many other reagents are usually available to effect a given transformation. Functional group exchange reactions generally have two functions in syntheses. Functional groups are (1) a structural feature of the final target, and (2) a necessary feature incorporated into a molecule that must be manipulated (transformed) to alter or form a carbon-carbon bond. Functional group interchange reactions are, therefore, very important in synthetic organic chemistry.

Many different types of reactions are used in functional group interchanges. We can categorize reactions according to the type of transformation, which is a subset of functional group interchanges. This categorization can help us understand when and how to use a particular reaction. Grouping reactions by similar or related mechanisms is very common.



The importance of functional group exchange reactions is illustrated by a simple synthetic problem, in which bromohydrin 2 is prepared from cyclohexanone (1). This particular synthesis

requires only functional group transformations. The synthetic relationship between 1 and 2 is represented in the diagram as $2 \Rightarrow 1$, which is meant to show that the bromohydrin can be formed from the ketone by an as yet unknown number of synthetic steps. Corey and co-workers^{1,2} called this representation *a transform*, and used it to define retrosynthetic relationships (sec. 1.2). If we analyze the $2 \Rightarrow 1$ relationship, it is clear that Br and OH must be incorporated on adjacent carbons, and one possibility is an addition reaction to an alkene. We must somehow convert the ketone to an alkene. One approach would involve reduction of the carbonyl to an alcohol, which could be converted to a leaving group that would allow an elimination reaction to give the alkene. This analysis is based on the synthetic conversion of 1 to 2, and the reaction types suggested by this analysis leads to a choice of the reagents that are required for each transformation. Initial reduction of the ketone, with a suitable reducing agent such as LiAlH₄ (sec. 4.2.B) gives alcohol **3**. Subsequent reaction with phosphorus tribromide (sec. 2.8.A) gives bromide 4, in what is known as a substitution reaction. Base induced elimination gives alkene 5, which illustrates both elimination and an acid-base reaction. The final reaction with bromine and water (sec. 2.10.C) gives 2, and illustrates an addition reaction. This sequence used five major reaction types: acid-base, reduction, substitution, elimination, and addition. Te reaction types used for functional group exchanges are collected into seven traditional categories:

1.	Acid - base reactions	$HA + B \longrightarrow HB + A$
2.	Substitution reactions	$RX + A \longrightarrow RA + X$
3.	Elimination reactions	$X-C-C-Y \longrightarrow C=C + X-Y$
4.	Addition reactions	$C=C + X-X \longrightarrow X-C-C-X$
5.	Nucleophilic acyl addition	C=O → Nuc-C-O-E
6.	Oxidation reactions	An example is H-C-O-H \longrightarrow C=O
7.	Reduction reactions	An example is C=C \longrightarrow H-C-C-H

Most functional group exchanges and transformations fall into one of these seven categories, which it is useful for classification of reagents, as in Table 2.1.³ Many reactions can be placed into more than one of these simple categories. Elimination reactions, for example, involve an initial removal of hydrogen by a base (an acid-base reaction). Addition reactions are two-step reactions that involve a substitution. Oxidation and reduction reactions constitute such a large proportion of functional group exchanges that they will be discussed in separate chapters (chaps. 3 and 4, respectively), to properly examine their synthetic applications. This chapter

^{1.} Corey, E.J.; Cheng, X. The Logic of Chemical Synthesis, Wiley Interscience, New York, 1989.

 ⁽a) Corey, E.J.; Wipke, W.T. Science, 1969, 166, 178; (b) Corey, E.J.; Long, A.K.; Rubinstein, S.D. Ibid 1985, 228, 408; (c) Corey, E.J.; Howe, W.J.; Pensak, D.A. J. Am. Chem. Soc. 1974, 96, 7724; (d) Corey, E.J. Quart. Rev. Chem. Soc. 1971, 25, 455; (e) Corey, E.J.; Wipke, W.T.; Cramer, III, R.D.; Howe, W.J. J. Am. Chem. Soc. 1972, 94, 421; (f) Corey, E.J.; Jorgensen, W.L. Ibid 1976, 98, 189.

^{3.} Many examples of these types of reactions are found in Larock, R.C. *Comprehensive Organic Transformations*, 2nd Ed. Wiley-VCH, New York, *1999*.

will begin with the first five reaction types to discuss their application to chemical reactions, synthesis, and functional group transformations. The ultimate goal is to establish a firm base upon which to introduce both the reactions required for making important carbon-carbon bonds, and also the techniques employed by the modern synthetic chemist.

Substitution ($S_N 1$ or $S_N 2$) is a reaction where one functional group attached to n aliphatic carbon is replaced by another called a **nucleophile** (nucleophilic aliphatic substitution). Nucleophiles can also form a new bond to an acyl carbon (nucleophilic acyl addition). Both of these **retrosynthetic transforms** are represented by the C-Nuc species, where Nuc = CN^- , AcO^- , RO^- , N_3^- , CO_2^- , etc. and X = Cl, Br, I, OAc, OSO_2R , etc., for $S_N 2$ reactions. In nucleophilic acyl substitutions, the nucleophile is usually a carbon, nitrogen or oxygen species.



Class of Reagent (Reaction Type)	Reagents
Acids (acid-base; addition)	HCl, HBr, HF, HI, H ₂ SO ₄ , HNO ₃ , H ₃ PO ₄ , RCO ₂ H, RSO ₃ H, HOH, ROH, AlX ₃ , FeX ₃ , ZnX ₂ , SnX ₄
Bases (acid-base; elimination)	NaOH, KOH, LiOH, Ca $(OH)_2$, NaH, KH, RO–M+ (<i>t</i> -BuO, MeO, EtO; M = Na+, K+), RLi, RMgX, NH ₃ , R ₃ N, NaNH ₂ , LiNH ₂ , NaNR ₂ or LiNR ₂ (HNR ₂ + Na or Li), HOH, ROH, ROR
Nucleophiles (substitution; nucleophilic acyl substitution)	MX (X=Cl ⁻ , Br ⁻ , I ⁻ , CN ⁻), HO ⁻ , RO ⁻ , NH ₂ ⁻ , NR ₂ ⁻ , RC=X ⁻ , R(CO), HS ⁻ , RS ⁻ ; M=Na ⁺ , K ⁺ , Li ⁺ , RLi, RMgX, NH ₃ , NR ₃ , HOH, ROH, R ₂ CuLi
Oxidizing agents (oxidation; addition; acid-base)	$CrO_3, K_2Cr_2O_7, H_2O, ROOR, HCrO_4, KMnO_4, Cu/heat, MnO_2, SeO_2, HIO_4, O_3, NaOX(NaOH/X_2), NBS, NCS, RCO_3H, HONO (NaNO_2/HX), HNO_3, H_2SO_4, Ag^+, Cu_2^+$
Reducing agents (reduction; addition)	Sn/HCl, Fe/HCl, H ₂ + catalyst, (Pd, Pt, Ni(R), Ru), NaBR ₄ (R=H, alkyl, OR), LiAlR ₄ (=H, alkyl, OR)

Reagents that are classified as bases can be used with both Lewis and Brønsted-Lowry acids, and one application is the elimination of alkyl halides (E2 reactions; sec. 2.9.A) in the presence of a base. Elimination involves conversion of a saturated moiety containing a leaving group to

a molecule with a multiple bond. An example of this latter transform is:

$$C:C' \longrightarrow H \cdot C \cdot C \cdot X$$
 elimination

where the leaving group (X) is OH, halogen, OTs, and so on. The E2 reaction is discussed in section 2.9.A. Note that another class of elimination reactions includes polar species such as sulfoxides, amine oxides, and selenoxides, which undergo thermal syn elimination (sec. 2.9.C).

Acid-base reactions are among the most general that are known. They are used to generate reactive intermediates that can be part of other reaction types. Both Lewis and Brønsted-Lowry bases donate two electrons to an acid. Acid-base reactions are integral to many reactions, although they are not always easy to describe by a specific transform since they may be an adjunct to the desired transformation. An example is the use of conjugate bases of acids as nucleophiles in substitution reactions. Typical reactions that generate nucleophiles are HCN \rightarrow CN⁻ and HN₃ \rightarrow N₃⁻. Conjugate bases of weak acids are usually required to initiate E2 type reactions, and typical examples are ethoxide and amide bases from the reactions EtOH ® EtO⁻ and HNEt₂ \rightarrow LiNEt₂. Many reagents that add to alkenes are acids (HCl, HOBr, etc.), and the reaction mechanism for these reactions begins with the alkene reacting as a base, donating two electrons to the acid (H⁺). Addition reactions involve the transformation of sp hybridized carbons to sp² or to sp³, or the transformation of sp² hybridized carbon atoms to sp³. Addition reactions that add strong protonic acids HX, or diatomic bromine, chlorine, etc. to alkenes, are common in synthesis. The retrosynthetic transform can be generalized as:

As each of these reaction types is discussed in later sections, it will be apparent that virtually all substrates that are functionally transformed are polarized or contain π bonds. Pericyclic reactions will be presented in Chapter 11, and are an important exception. When analyzing a substrate for a functional group transform, the following criteria are usually important.

- 1. Examine the degree and direction of polarization of a bond. Where will the electrons go?
- 2. How many bonds away will the polarization be effective?
- 3. What is the attraction of a given reagent for the polarized bond?
- 4. Does the polarized bond contain more than one leaving group.
- 5. If there is a π bond, how efficiently can it donate electrons.
- 6. If the π bond is polarized, will the δ + center undergo substitution or will the δ pole act as an electron donor.
- **7.** Does the reactive center possess special strain or steric hindrance that will modify the reactivity?
- **8.** Is the reactive center conjugated?

Perhaps most importantly,

9. Is there more than one reactive center in the molecule and can more than one reaction occur competitively?

2.2. BRØNSTED-LOWRY ACIDS AND BASES

Many organic molecules react via an initial acid-base reaction that is formally classified by a Brønsted-Lowry definition. Remember that a Brønsted-Lowry acid is a proton donor and a Brønsted-Lowry base is a proton acceptor. The key to this definition is an understanding that there is a proton transfer and change the focus to understand that a base removes the proton from the acid by donating two electrons to the proton. We are therefore looking for proton donors and acceptors, and specifically for molecules that donate electrons to a protonic acid to form a new bond to that hydrogen atom. Understanding the properties of acid-base equilibria is an aid to understanding the mechanistic details of many different reactions.

2.2.A. Acidity in Organic Molecules

The reaction of HA and B to give BH^+ and A^- is the general expression written for acid-base reactions. The acid (HA) reacts with a base (B:) to give the conjugate acid HB⁺ (CA) and a conjugate base, A^- (CB). The hydrogen atom is transferred to B: as a proton (H⁺). Since the product HB⁺ is also an acid and A^- is a base, they react to establish an equilibrium. The position of the equilibrium is given by the equilibrium constant K, where K_a is used for acidbase reactions. A small value of K_a represents little ionization of HA, which means that the equilibrium is shifted to the left and this shift is associated with decrease in the acidity of HA. In other words, if the equilibrium lies to the left, HA did not react with the base (B) to any great extent and it is considered to be a weaker acid. If K_a is large, HA reacted with B to produce BH⁺ and A⁻, so the equilibrium is shifted to the right and HA is considered to be a stronger acid. The position of the equilibrium is dependent on many factors, including the solvent. A more convenient way to express the relative strength of an acid is pK_a . A large K_a is equivalent to a small pK_a so as the pK_a decreases, the acid strength increases. Note that our definition of a strong acid (large K_a) implies that the reaction of HA and B is more facile than the reverse reaction of BH⁺ and A⁻. Conversely, a weak acid (small K_a) implies that the reaction of BH⁺ and A⁻ is more facile than that of HA and B.

HA + B
$$\xrightarrow{K_a}$$
 BH⁺ + A⁻
 $K_z = \frac{[HB^+] [A^-]}{[HA] [B:]}$ where pK_a = $-\log k_a$ and K = 10^{-pK_a}

Many organic compounds such as carboxylic acids, phenols and 1,3-dicarbonyl compounds are acids, but they are typically much weaker than the familiar mineral acids HCl or H₂SO₄. Likewise, many organic compounds (particularly amines and phosphines) are bases, but such bases are generally weaker than alkali bases such as NaOH. Amphoteric compounds such as alcohols are common. Alcohols are weak acids in the presence of a strong base, but they are weak bases in the presence of a strong acid. This chemical reactivity can be exploited in many chemical transformations. In the reaction of 3-pentanol (6) and H⁺ (HCl), the initial product is oxonium ion (7). Relating this reaction to the generic acid-base reaction shown above [HA] is the acid catalyst (HCl), [B] is the oxygen atom of 3-pentanol, the chloride ion is [A⁻] (the gegenion of the acid catalyst), and [HB⁺] is Et₂CH-OH₂⁺ (7). An acid catalyst that is strong enough to react with the alcohol, which is a weak base, initiates the reaction. In other words, the acid catalyst must be a stronger acid than the OH unit of the alcohol. In this particular reaction 7 is formed and reacts with the nucleophilic chloride ion at carbon, with loss of the leaving group water to give 3-chloropentane as the final product.



Ethers are weak bases. Although they are commonly used as solvents, diethyl ether and THF are weak bases in the presence of a strong acid and THF is a stronger base than diethyl ether. The relative base strength can be seen upon examination of the experimentally determined acidity of the conjugate acid derived from diethyl ether [Et₂OH⁺], which has a $pK_a = -3.12.^4$ This acid is stronger than the protonated form of THF [C₄H₈OH⁺], which has a $pK_a = -2.08.^4$ In reactions where the ether behaves as a Lewis base, as in Grignard reactions (sec. 8.4.A) or hydroboration (sec. 5.2.A), understanding the relative basicity is important.

The hydrogen on the α -carbon of a ketone such as 2-butanone is an important weak acid in organic chemistry. When 2-butanone (A) reacts with sodium ethoxide (B), the conjugate base is enolate anion **8** (CB), and ethanol is the conjugate acid (CA). Ethanol (pK_a about 17) is a stronger acid than the ketone (pK_a about 19-20) and will react with the basic enolate to regenerate the ketone and shift the equilibrium back to the left. The net result is an equilibrium

 ⁽a) Arnett, E.M.; Wu, C.Y. J. Am. Chem. Soc. 1960, 82, 4999; (b) Arnett, E.M.; Wu, C.Y. Ibid 1962, 84, 1680, 1684; (c) Deno, N.C.; Turner, J.O. J. Org. Chem. 1966, 31, 1969.

solution that contains enolate **8**, ethanol, 2-butanone, and NaOEt (sec. 9.2.E).⁵ It is important to note that in any acid-base reaction, HA does not function as a Brønsted-Lowry acid unless a sufficiently strong base (B) is present to remove and accept the acidic proton. If the base under consideration is too weak, the equilibrium is shifted almost exclusively to the left (i.e., we call HA a weak acid).

When comparing two acids, several factors can be used to evaluate relative acid strength. In an acid-base reaction where acids are on both sides of the equilibrium (A and CA from above), this information can be useful to estimate the position of the equilibrium, which is essentially an estimation of K_{a} .

1. In general, a strong acid generates a weak conjugate base and, conversely, a weak acid generates a strong conjugate base.

Comparison of HCl and NH₃ indicates that HCl is a strong acid that generates the weak base, Cl⁻:

$$HCl \rightarrow H^+ + Cl^-$$

Conversely, ammonia is a weak acid that generates the strong base, NH₂⁻.

$$NH_3 \rightarrow H^+ + Cl^-$$

A base will usually deprotonate an acid that has a pK_a lower than its own conjugated acid, and the extent to which the reaction produces products if the main criterion for labeling a base as strong or weak.

2. Across the periodic table, acidity of an X-H species generally increases from left to right.⁶

weak acid $CH_4 < NH_3 < H_2O < HF$ strong acid $pK_a ~(\approx 50) ~(\approx 31) ~(15.7) ~(3.17)$ strong conj. base $CH_3^- > NH_2^- > HO^- > F^-$ weak conj. base

 ⁽a) House, H.O. Modern Synthetic Reactions, 2nd Ed. W.A. Benjamin, 1972, pp 452-595; (b) House, H.O.; Phillips, W.V.; Sayer, T.S.B.; Yau, C.C. J. Org. Chem. 1978, 43, 700; (c) Etheredge, S.J. Ibid 1966, 31, 1990; (d) House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. Ibid 1969, 34, 2324; (e) House, H.O.; Gall, M.; Almstead, H.D. Ibid 1971, 36, 2361.

^{6.} Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry*, 3rd Ed. Harper and Row, New York, *1987*, pp 297-298.

A consequence of this trend in acidity is that basicity increases from right to left across the periodic table.

3. Acidity increases going down the periodic table, despite a decrease in electronegativity.

Based on rule 3, basicity increases going up the periodic table. Fluoride is smaller and more electronegative than iodide, has a greater attraction for protons, and forms a stronger covalent bond. These factors make it more difficult to lose a proton from HF than from HI, hence, the equilibrium is shifted to the left relative to HI, and HF is a weaker acid. Clearly, the increased size of the iodine atom leads to a greater H-I bond distance and, due to the resultant decrease in internuclear electron density, a weaker bond. The acid strength increases, since the weaker I-H bond is more easily ionized, which ignores solvation effects, however, as well as product stability, which are critical to this analysis (see below). However, *we must look at the both the starting materials and the products to determine the position of the equilibrium, and thereby the relative acidity.* The iodide ion is larger than the fluoride ion and the charge is dispersed to a great extent, leading to greater stability. The larger ions are also more easily solvated, again leading to greater stability. Greater stability of one product relative to the other means the equilibrium is shifted further to the right for HI-iodide, and this leads to HI being a stronger acid.

These three concepts allow a quick inspection of a simple acid (HX) for its relative acid strength. Experimental analysis of the acids commonly encountered in organic reactions requires knowledge of at least three factors: (1) electronic effects, (2) resonance effects, and (3) solvent effects.

The presence of an electron-donating or an electron-withdrawing heteroatom (or group) on a carbon induces bond polarization through adjacent carbon atoms in a chain, as illustrated by **9** (first introduced in section 1.3).⁸ Electron-donating groups release electrons via inductive or field effects, leading to the so-called +*I* effect. Conversely, an electron-withdrawing group removes electron density, the so-called –*I* effect. With respect to an acid, the +*I* effect lowers the acid strength whereas the –*I* effect raises it. Electronic effects are described by the inductive model^{9,10} and the field effect model.^{9,11}

^{7.} Smith, M.B.; March, J. March's Advanced Organic Chemistry, 6th ed.; Wiley, New York, 2007, pp 384, 375.

 ⁽a) Seebach, D. Angew. Chem. Int. Ed. 1979, 18, 239; (b) Cram, D.J.; Cram, J.M. Chem. Forsch. 1972, 31, 1 [Chem. Abstr: 77:163690d 1972].

 ⁽a) Baker, F.W.; Parish, R.C.; Stock, L.M. J. Am. Chem. Soc. 1967, 89, 5677, (b) Golden, R.; Stock, L.M. Ibid 1966 88, 5928, (c) Holtz, H.D.; Stock, L.M. Ibid 1964, 86, 5188.

^{10.} Branch, G.E.K; Calvin, M., The Theory of Organic Chemistry, Prentice Hall, New York, 1941, Chapter 6.

^{11. (}a) Kirkwood, J.G.; Westheimer, F.H. J. Chem. Phys. 1938, 6, 506; (b) Westheimer, F.H.; Kirkwood, J.G. Ibid 1938, 6, 513.

The inductive model assumes that substituent effects are propagated by the successive polarization of the bonds between the substituent and the reaction site (as in 9). This effect is transmitted through the σ bond network (σ inductive effect) as well as the π -bond network (π inductive effect).¹⁰ The field effect model assumes that the polar effect originates in bond dipole moments, and is propagated according to the classical laws of electrostatics. The appropriate description of this effect is the **Kirkwood-Westheimer model**,¹¹ in which the molecule is treated as a cavity of low dielectric constant submerged in a solvent continuum.^{9a}

Attempts to distinguish inductive and field effects have been frustrated by the lack of a molecule that provides an unambiguous answer.^{9b} Such a molecule would require that the low dielectric cavity of the field effect model¹² be occupied by the chemical bonds important to the inductive effect model.¹⁰ For example, o-chlorophenylpropionic acid is weaker than expected by the inductive model.¹² If a small attenuation factor is adopted for through-bond transmission of the polar effect, both models predict similar results.¹³



Stock reported the pK_a of two systems, 10^{9c} and 11,^{9b} that allow the field effect to be studied, and deter-mined that the dominant term associated with the change in pK_a was the positive charge, transmitted through the cavity.^{14a} This finding is in general agreement with the Kirkwood-Westheimer model,¹¹ which suggests that the field effect is the dominant term.⁹ Ammonium salts have an -I effect,¹⁵ which lowers pK_a (strengthens the acid) relative to acetic acid.¹⁶ Due to the localized character of the σ electrons, the inductive effect in this system diminishes with increasing distance between separation of substituent and reaction center. The change in pK_a is actually due to a combination of inductive, steric and hyperconjugative influences. Chloroacetic acid (pK_a = 2.87)¹⁷ can be compared with propionic acid (pK_a = 4.76), since there is no change in the number of α hydrogens, no steric or hyperconjugative effect, and the inductive effect is the only significant contribution to pK_a.¹⁴ The -I effect of chlorine induces a significant reduction in pK_a (stronger acid). Electron releasing groups with a +*I* effect will

16. Reference 15, see Chapter 14 therein.

^{12. (}a) Roberts, J.D.; Carboni, R.A. J. Am. Chem. Soc. 1955, 77, 5554; (b) also see Wells, P.R.; Adcock, W. Australian J. Chem. 1965, 18, 1365.

^{13.} Ehrenson, S. Progr. Phys. Org. Chem. 1964, 2, 195.

^{14. (}a) Dewar, M.J.S.; Grisdale, P.J. J. Am. Chem. Soc. 1962, 84, 3539, 3548; (b) Murrell, J.N.; Kettle, S.F.A.; Tedder, J.M. Valence Theory, John Wiley, Londo, 1965, Chapter 16.

^{15.} Brown, H.C.; McDaniel, D.H.; Hafliger, O. *Determination of Organic Structures by Physical Methods*, Ed. Braude, E.A.; Nachod, F.C., Academic Press, New York, **1955**, p 569.

^{17.} Bolton, P.D.; Hepler, L.G. Quart. Rev. Chem. Soc. 1971, 25, 521.

have the opposite effect and lead to a decrease in acidity.¹⁴



The fundamental concept of inductive and field effects introduced for carboxylic acids can be applied to weaker acids such as the α -hydrogen of ketones. Reaction of **12** with the strong base lithium diisopropyl amide (LDA) in Zoretic and co-worker's synthesis of megaphone¹⁸ illustrates this premise. Both H_a and H_b in **12** are acidic, but H_a has a lower pK_a by virtue of its proximity to the carbonyl (secs. 9.1, 9.2) and is removed preferentially. The conjugating effect of the π bond makes H_b acidic (it is a *vinylogous* acid), but that acidity is diminished due to the distance from the carbonyl. Formation of the enolate anion of **12** was followed by alkylation (secs. 2.6.A, 9.3.A) to provide **13** in good yield.

It is of paramount important to remember that acid-base reactions are equilibrium reactions, where the position of the equilibrium (K_a) is determined by the interactions of the acid-base pair A and B and the acid-base pair on the other side of the reaction (CA and CB). One cannot discuss the acidity of a molecule without considering the products formed by the reaction. For example resonance delocalization in the final product makes that product more stable relative to a competing reaction or even a different reaction where the product is not resonance stabilized. The result is that the resonance-stabilized product helps to shift the reaction equilibrium to the right, towards that product. Resonance stabilizes the product due to the existence of low energy molecular orbitals that lead to p electron delocalization, transmitted over unsaturated systems. Electron delocalization diminishes the net charge, leading to additional stabilization. This effect is clear when acetic acid and methanol are compared as acids. Acetic acid (pK_a , 4.76) owes its greater acidity, in part, to the resonance stabilized acetate anion (14), whereas methanol $(pK_a, 18)$ generates the methoxide anion (15). The charge is *localized* on the oxygen atom in methoxide, but is *delocalized* over three atoms in the acetate anion. Delocalization of charge lowers the net energy of the system, making it more stable (and thereby, less reactive). The increased stability of the conjugate base of acetic acid (the acetate anion) shifts the equilibrium towards the products to a much greater extent than is possible in the methanol reaction (which generates the methoxide anion). A shift to a higher concentration of products is reflected by a larger K_a, which means a lower pK_a for acetic acid relative to methanol.

^{18.} Zoretic, P.A.; Bhakta, C.; Khan, R.H. Tetrahedron Lett. 1983, 24, 1125.



Resonance effects can also be transmitted via the π bonds of aromatic rings. A comparison of phenol (p K_a , 10.0), 4-nitrophenol (p K_a , 7.2) and 2,6-dinitrophenol (p K_a , 3.6) shows that the presence of a nitro group enhances acidity, in part by delocalizing electron density in the conjugated phenoxide base. Removal of the acidic proton of phenol leads to the resonancestabilized anion **16**. The presence of a nitro group at C4 leads to delocalization of the charge on the nitro group (see **17**) and increased resonance stability. A second nitro group at C2 or C6 (as in 2,6-dinitrophenol) will lead to greater resonance stability and enhanced acidity of that phenol. In other words stabilization of the anion by nitro substituents is reflected in the p K_a values.

Table 2.2. Influence of Solvents on the Acidity of Common Protonic Acids

]	рК		
	in HOH	in MeOH	in DMF	in DMSO	in MeCN
O₂N - ◯ → OH	7.15	11.2	10.9	9.9	7.0
MeCO ₂ H	4.76	9.6	11.1	11.4	22.3
\bigcirc -CO ₂ H	4.20	9.1	10.2	10.0	20.7
[Reprinted with permission from Clare, B.W.; Cook, D.; Ko, E.C.F.; Mac, Y.C.; Parker, A.J., J. Am. Chem. Soc., 1966 , 88, 1911. Copyright © 1966 American Chemical Society.]					

The acidity of a compound changes with the polarity of the solvent, and is different in protic versus aprotic solvents. Table 2.2,¹⁹ compares the pK's of several acids in various solvents.²⁰ Most reactions take place in solution rather than in the gas phase,²⁰ and the factors that account for the enormous differences between solution and gas-phase chemistry are operationally

 ⁽a) Clare, B.W.; Cook, D.; Ko, E.C.F.; Mac, Y.C.; Parker, A.J. J. Am. Chem. Soc. 1966, 88, 1911; (b) Kolthoff, I.M.; Chantooni, Jr., M.K.; Bhowmik, S. Ibid 1968, 90, 23.

^{20.} Arnett, E.M. Acc. Chem. Res. 1973, 6, 404.

defined as **solvation**.¹⁹ Protic solvents facilitate charge separation, and solvation of both the conjugate acid and conjugate base can shift the equilibrium to the right (the compound is more acidic). Aprotic solvents effectively solvate only the cationic product but this can influence the equilibrium and the acids in Table 2.2 show enhanced acidity in the more polar DMSO, relative to DMF. Solvating ability is not the only factor however. Acidity is diminished in methanol due to decreased hydrogen-bonding, relative to the acidity in water. Basicity of the solvent is an important factor. A comparison of aprotic solvents (DMF, DMSO, and acetonitrile) shows that the more basic the solvent, the greater the apparent acidity of HA. This effect is due, in part, to disruption of the internal hydrogen bonding of HA.²¹

In later chapters (particularly chapters 8 and 9), we will examine carbon acids (C-H) that generate carbanions as the conjugate base. The solvent plays a critical role in the relative pK_a of carbon acids (15.8 for phenylacetylene in diethyl ether, 26.5 in DMSO for example).²² In this particular example, the difference in pK_a is explained by the extent of ion-pairing or ion aggregation. The equilibrium for the deprotonation of phenylacetylene is also shifted to the right when the solvent is changed from cyclohexylamine ($pK_a = 20.5$) to diethyl ether due to increased stability of the ion pair (for the potassium anion, $PhC=C^-K^+$) or the ion aggregate ($PhC=C^-K^+$)_n.

It is apparent that acidity in organic molecules is influenced by several factors. Among these, inductive effects, solvent effects, and effects that influence the stability of both the acid and the conjugate base are important. The base is obviously important since the strength of an acid is directly dependent on the strength of the base.

2.2.B Basicity in Organic Molecules²³

Since the base is part of the acid-base equilibrium, the relative strength of a base is determined by the position of the equilibrium and is influenced by the same factors discussed for acids. For common bases, base strength *increases* going to the left and up in the periodic table. An example is

$$F^- > Cl^- > Br^- > I^-$$

Base strength is usually expressed by the pK_a of its *conjugate acid*, BH^+ according to the equation

$$BH^+ = B: + H^+ \qquad K_a = \frac{[B:] [H^+]}{BH^+}$$

^{21.} Grunwald, E.; Ralph, E.K. Acc. Chem. Res. 1971, 4, 107.

^{22.} Bordwell, F.G.; Matthews, W.S. J. Am. Chem. Soc. 1974, 96, 1214.

^{23.} Clark, J.; Perrin, D.D. Quart. Rev. Chem. Soc. 1964, 18, 295.

Table 2.3. +*I*, +*R*, -*I* and -*R* Effects in Bases

	Effect	Examples
+I	(base strengthening)	RO^- , R_2N^- , alkyl
<i>–I</i>	(base weakening)	SO_2R , NH_3^{\pm} , CF_3 , NO_2 , CN , Cl , Br CO_2H , CO_2R , I, COR , SR , Ph , NR_3^+
+R	(base strengthening)	F, Cl, Br, I, OH, OR, NH ₂ , NR ₂ NHCOR, O ⁻ , HN ⁻ , Me, alkyl
- <i>R</i>	(base weakening)	NO_2 , CN^- , CO_2H , CO_2R , $CONH_2$, Ph , COR , SO_2R

The inductive and field effects lead to +I (electron donating groups, base strengthening) and -I effects (electron withdrawing groups, base weakening). Examination of amines shows that electron releasing groups intensify the electron density around nitrogen, and to a first approximation, this enhances basicity. Electron-withdrawing groups should have the opposite effect. Resonance effects (+*R*) also apply, as described earlier for acids. Resonance effects are also known as **mesomeric** effects (+*R* is +*M*; -*R* is -*M*), as described in the discussion of aromatic substitution in section 2.11. Electron donating groups can be characterized as having +*R* effects, and electron-withdrawing groups as having -*R* effects. When comparing 4-nitroaniline and 4-methylaniline, the methyl group is electron releasing (+*R*) but the nitro group is electron withdrawing (-*R*). The +*R* effect of the methyl is transmitted through the aromatic ring, intensifying the electron density on nitrogen and increasing the basicity.

The *I* and *R* effects may operate in opposite directions. An example is a slight resonance effect of a group in the meta position of an aromatic nucleus, where the inductive effect is rather large. In the para position, the resonance effect is also large. Table 2.3^{24} correlates several substituents with *I* and *R* effects.

There are two categories of steric hindrance around the basic atom that influence relative base strength.

- 1. **Primary steric effect.** Steric impedance to protonation occurs when bulky groups surround the basic center. When this results in greater strain in the cationic conjugate acid produced upon protonation than in the neutral molecule, the base is weaker.²⁵
- 2. Secondary steric effect. There is hindrance to solvation and it is base weakening.

The primary steric effect is credited with the greater basicity of aniline relative to 2,6-

^{24. (}a) Trotman-Dickenson, A.F. J. Chem. Soc. **1949**, 1293, (b) Arnett, E.M.; Jones III, F.M.; Taagepera, M., Henderson, W.G., Beauchamp, J.L.; Holtz, D.; Taft, R.W. J. Am. Chem. Soc. **1972**, 94, 4724.

^{25.} Taft, Jr., R.W Steric Effects in Organic Chemistry, John Wiley, New York, 1956, Chapter 13.

dimethylaniline, due to greater steric inhibition for reaction with a proton. The secondary effect is probably responsible for the difference in basicity between *N*,*N*-diethylaniline (pK_a , = 6.65) and *N*,*N*-dimethylaniline (pK_a , = 5.8). The two ethyl groups inhibit solvation of the protonated conjugated acid,¹⁶ which is the ammonium salt. Solvation varies with the available space around the basic center, and should be less for pyridine than for aniline. The diminished basicity of tertiary amines relative to secondary amines in solution has been attributed to this effect.^{24a}

It has been known for many years that the proton acceptor ability of amines in solution [expressed as pK_a of the conjugate acid (BH⁺)] takes the order:¹⁹ NH₃ < R₃N < RNH₂ \approx R₂NH. This anomalous order is understood in terms of two opposed influences, one base strengthening and the other base weakening. The base strengthening effect is the electron releasing inductive effects of the alkyl groups on nitrogen. This effect should make tertiary amines more basic when compared to secondary or primary amines. As described immediately above, the other major influence is solvation. Solvation is greatest for the ammonium salt produced from primary amines, leading to greater stabilization and enhanced basicity. Using high pressure mass spectrometry (there are no solvation effects), Munson demonstrated the order of gas-phase basicity is:²⁶ NH₃ < RNH₂ < R₂NH < R₃N.

It was assumed that the inversion of base strength in solution was primarily a solvation phenomenon. Indeed, this effect is largely the result of hydrogen bonding in an aqueous solvent when comparing ammonia $(NH_3 \rightarrow NH_4^+)$ with four sites for hydrogen-bonding in the ammonium salt versus a tertiary amine $(R_3N \rightarrow R_3NH^+)$, with only one site for hydrogen bonding in the ammonium salt. The larger the number of alkyl groups on nitrogen leads to fewer protons in the ammonium salt, and diminished hydrogen bonding. This structural feature works in opposition to the electron-releasing effect of the increasing number of alkyl groups and dispersal of charge by the inductive effect.²⁴

Clearly, a discussion of relative acidity or basicity must specify the solvent. The actual order of basicity for amines in solvents, however, is a combination of inductive and solvation effects. Steric hindrance around the electron pair on nitrogen also plays an important role (see above). When all of these factors are accounted for, secondary amines tend to be the most basic, as shown above.

The p*K* of several common amines used in synthesis have been determined in THF at 25°C.²⁷ 4-*N*,*N*-Dimethylaminopyridine (DMAP, **18**), proton sponge (**19**), quinuclidine, (**20**), DBU (1,8-diazabicyclo-[5.4.0]-undec-7-ene, **21**),^{28b} and diazabicyclo-[2.2.2]octane (DABCO, **22**) are shown, along with triethylamine, tributylamine, and tribenzylamine for comparison.²⁷

^{26.} Munson, M.S.B. J. Am. Chem. Soc. 1965, 87, 2332.

^{27.} Streitwieser, A.; Kim, Y.-J. J. Am. Chem. Soc. 2000, 122, 11783 and references cited therein.

^{28.} For synthetic examples, see (a) Achab, S.; Das, B.C. J. Chem. Soc. Chem. Commun. 1983, 391; (b) Oediger, H.; Möller, Fr. Angew. Chem. Int. Ed. 1967, 6, 76.

The p*K* values for these bases are shown in THF, DMSO, and acetonitrile in Table 2.4,²⁷ determined from proton-transfer ion pairs of the type BH⁺ with acidic indicator hydrocarbons. The values obtained in THF differ substantially from the ionic pK_a values for NH⁺ in DMSO or acetonitrile. Streitwieser and co-workers²⁷ state that "at the present time amines cannot be placed quantitatively on any of the ion pair acidity scales currently in use for neutral acids in THF". The realization that it may be necessary to use different bases in different solvents, despite the fact that all are considered to be good bases in organic reactions, makes it clear why a quantitative comparison of bases is useful.



Many different types of bases are used in organic chemistry. Common inorganic bases include the anions of weak bases such as water and ammonia (hydroxide and amide: \neg OH and \neg NH₂). Similar deprotonation of alcohols leads to alkoxide bases (RO⁻). Methoxide (MeO⁻), ethoxide (EtO⁻), and *tert*-butoxide (Me₃C-O⁻) are very common, and are commonly used in the alcohol solvents from which they were made (methoxide in methanol, *tert*-butoxide in *tert*-butanol, etc.). Bases typically used to deprotonate water (p $K_a = 15.8$) or alcohols (p $K_a \sim 18$) are sodium hydride (NaH), potassium hydride (KH), sodium and potassium hydroxide [(NaOH, KOH), sodium metal [Na(0)], and sodium or potassium amide (NaNH₂ and KNH₂).

Table 2.4. pK values of several common amines in various solvents.

Amine	pK _a (THF)	pK _a (DMSO)	pK _a (MeCN)	
18	0.61		18.18	
19	2.15	7.47	17.28	
20	0.15	9.8	19.51	
21	-3.78		23.9	
22	0.80	8.93	18.29	
NEt ₃	2.11	9.0	18.70	
N(CH ₂ Ph) ₃	2,41	3.65	12.85	
NBu ₃	3.40		18.09	
[Reprinted with permission from Streitwieser, A.; Kim, YJ. J. Am. Chem. Soc. 2000, 122, 1, 1783. Copyright © 2000 American Chemical Society.]				



Amines are acids only in the presence of very strong bases that generate a conjugate acid that is significantly weaker than the amine. Amines are acids in the presence of Grignard reagents (R–MgX) and organolithium reagents (R–Li, secs. 8.4.G.iii and 8.5.G), which give amide bases (R₂N⁻M⁺) along with an alkane as the very weak conjugate acid (R-H). In a typical acid-base reaction, butyllithium is a strong base and diethylamine is the acid that gives lithium diethylamide (Et₂NLi) and the conjugate base and butane as the conjugate acid. Similarly, diisopropylamine gives lithium diisopropylamide (*i*-Pr₂NLi, often called LDA) and butane, and 2,2,6,6-tetramethylpiperidine (**23**) gives lithium 2,2,6,6-tetramethylpiperidide (**24**) and butane.²⁹ Since butane has a pK_a of >40, and the amines have pK_a values around 25, formation of the amide base is straightforward in these reactions.

The parent amine can be considered as amphoteric but it can function as a base only in the presence of acids that are considerably stronger than the ammonium salt of the base. In other words, triethylamine reacts with HCl to form triethylammonium chloride, where HCl is a much stronger acid than the ammonium salt, pushing the equilibrium in that direction. Triethylamine is a very weak base in the presence of a weak acid such as water, where the equilibrium favors the amine rather than the ammonium salt. Tertiary amines such as triethylamine (NEt₃) or pyridine (C₅H₅N, Py) are most commonly used as bases when an amine base is required, and these amines listed in Table 2.4. Imidazole (25) is an amine base used in systems that require a base that is weaker than triethylamine or pyridine. The stronger amide bases discussed above are used for deprotonation of weak acids (ketones, alkynes, esters, sulfides, etc., see Chaps. 8 and 9). The amide bases are often called non-nucleophilic bases due to their poor reactivity as nucleophiles in S_N2 (secs. 9.2.B, 2.7.C) and in acyl addition reactions (sec. 2.5). Their diminished nucleophilic strength results from the bulky alkyl substituents about the basic nitrogen which inhibits approach to carbon, but does not encumber approach to hydrogen. Two other non-nucleophilic bases are 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN, 26)^{28b} and DBU (21 from above),^{28a} in which the bridgehead nitrogen is sterically encumbered. When a very powerful base is required for deprotonation (pK_a of the acid

a very powerful base is required for deprotonation (pK_a of the acid is > 25), organometallic bases such as an organolithium reagent are used most often (sec. 8.5.G). Commercially available reagents such as butyllithium (BuLi), methyllithium (MeLi), and phenyllithium (PhLi) are commonly used in synthesis (see sec. 8.5.H).



The acid-base concepts described in this section focus on bases that react with protons, the classical Brønsted-Lowry definition of a base. There are other types of electron deficient or electron-donating molecules that do not involve transfer of protons. Such compounds are called Lewis acids or Lewis bases, respectively. The following section will discuss Lewis acids.

^{29.} Olofson, R.A.; Dougherty, C.M. J. Am. Chem. Soc. 1973, 95, 581.

2.3. LEWIS ACIDS

There are two working definitions of acidity and basicity. A **Lewis acid** is an electron pair acceptor and a **Brønsted-Lowry acid** is a proton donor. For basicity, a **Lewis base** is an electron pair donor and a **Brønsted-Lowry base** is a proton acceptor. Section 2.2.B focused primarily on the Brønsted-Lowry definitions and reactions of protonic acids (H⁺). This contrasts with a Lewis acid, which is an atom other than hydrogen that accepts two electrons from an electron donating species (the Lewis base). Group 13 atoms such as boron and aluminum are electron deficient since they can form only three covalent bonds and remain neutral. They can satisfy the octet rule by accepting an electron pair from a Lewis base, forming an adduct (a charged complex called an **ate complex**), as shown below. Such complexes will be of particular importance in hydride reductions (sec. 4.2.B) and in hydroboration reactions (see sec. 5.3, 5.4).

Transition metal salts are usually characterized by the presence of a metal atom that is capable of assuming multiple valences, and in many cases they can function as a Lewis acid. The relative order of Lewis acidity is not always straightforward since the electrophilic metal can have different valences and ligands (the groups or atoms attached to the metal). A number of general statements can be made, however.³⁰

Lewis acids usually take the form MX_n , where X is the ligand (a halogen atom, an amine or phosphine, CO, cyclopentadienyl, an alkene, etc.). The metal is M and *n* in X_n is the normal valency of M. The acid MX_n exhibits acidic properties in an equilibrium reaction with the base B (see above). Formation of a conjugate acid-base adduct (MX^-B^+ , the *ate* complex mentioned above) is characteristic of Lewis acid-base reactions. If chelation effects and double bond formation between M and any given atom of the base are excluded, three general statements can be made concerning acid strength.³⁰

- 1. In MX_n (n < 4) acidity arises from the central atom's requirement for completion of an outer electron octet by accepting one or more pairs of electrons from the base. Acidity is diminished when two electron pairs are required. There is a smaller energy gain upon receipt of the first pair and an accumulation of negative charge on M if two pairs are received. Therefore, Group 13 acids are more acidic than transition metal acids: $BF_3 > AlCl_3 > FeCl_3$
- 2. The acidity of M will decrease within any group with increasing atomic volume (effectively, with increasing atomic number) owing to the weaker attraction between

^{30. (}a) Satchell, D.P.N.; Satchell, R.S. Chem. Rev. 1969, 69, 251, (b) Idem Quart. Rev. Chem. Soc. 1971, 25, 171.

nuclear charge and incoming electron pairs (**Fajans' rules**).^{30a} The result of these effects leads to the order: $BX_3 > AIX_3 > GaX_3 > InX_3$

3. In general, the energies of different atomic orbitals lie closer together with increasing atomic number, because orbital contractions arising from the electronegativity of the nucleus tend to decrease with increasing atomic number. As a result, there is more effective overlap of hybridized orbitals. The availability of *d* orbitals will be easier (especially with *d* outer orbitals) and more effective, the heavier the element. This leads to a decrease in acidity, as in the series (B \rightarrow Al \rightarrow Ga \rightarrow In) above.

These three statements are taken directly from the review by Satchell and Satchell,³⁰ and can be used to estimate the strength of Lewis acids according their Group in the Periodic Table.³⁰

- a. Group 11 (Cu, Ag, Au) and 12 (Zn, Cd, Hg) usually give covalent species MX_2 : (ZnCl₂, CdI₂, etc.); M has four electrons in the outer group and needs two additional pairs. By rule 1 these should have only moderate acidity and by rule 2: ZnCl₂ > CdCl₂ > HgCl₂
- **b.** Group 13 (B, Al, In, Tl) and 3 (Sc, Y, La, Ac) by rule 1 tend to form the most acidic compounds (MX₃). The metal (M) requires only one electron pair to complete the octet (BF₃, AlCl₃, GaBr₃, etc.). Rule 2 is then applied.

 $BF_3 > AlCl_3 > GaBr_3 > InCl_3 > TlCl_3$ and, $ScCl_3 > YCl_3 > LaCl_3$.

- **c.** Group 14 (C, Si, Ge, Sn, Pb) and 4 (Ti, Zr, Hf) form covalent species such as MX₄. There are no acidic properties when M = C, and when M = Si only weak acidic properties are observed.
- d. Group 15 (N, P, As, Sb, Bi) and 5 (V, Nb, Ta) usually take the form MX₃ or MX₅. When M is nitrogen, there are no acidic properties, indeed these are bases. When M is phosphorus the molecule is a weak base, but the octet can expand to give weakly acid properties in some reactions. In general, MX₅ compounds are more acidic than Groups 15 and 5 MX₃ compounds due to the expanded octet and the utilization of d orbitals. Notethat both SbX₅ and NbX₅ are powerful acids.
- e. Group 16 (O, S, Se, Te, Po) and 6 (Cr, Mo, W) have the normal covalent character of MX₂. There are close parallels with Groups 14 and 4. Both OX₂ and SX₂ have virtually no acidity and TeX₂ is very weak. Species arising from abnormal valences, such as TeX₄, can exhibit enhanced acidity since only one electron pair is then required to complete the outer shell of 12.
- f. Group 17 (F, Cl, Br, I, At) and 7 (Mn, Tc, Re) resemble 14 and 4 and 16 and 6 in

that the lower members are only weakly acidic. The higher members can expand the octet when attached to electron-withdrawing substituents, and have enhanced acidity $(I_3^- \text{ and } Ph\text{-ICl}^-)$.³¹

With these six general statements as a guide, it is possible to order the more common Lewis acids by decreasing acid strength: $BX_3 > AIX_3 > FeX_3 > GaX_3 > SbX_5 > InX_3 > SnX_4 > AsX_5 > SbX_3 > ZrX_4$

The relative strength of Lewis acids is important to many major classes of organic reactions utilized in synthesis. In sections 11.6.A and 12.4, Lewis acids will be used in connection with several important carbon-carbon bond forming reactions. These include Friedel-Crafts type reactions³² and **Diels-Alder reactions**^{33,34,35} (sec. 11.4.A), as well as other pericyclic reactions (chap. 11). Changing the Lewis acids can have dramatic effects on the rate of reaction, regioand stereoselectivity, and product distribution in both the Diels Alder and Friedel-Crafts reactions.³² If the Lewis acid is too reactive, degradation of products or starting materials can be a serious problem. For these reasons, several Lewis acids covering a wide range of acid strengths should be available for a synthesis. Aluminum chloride is a very reactive and unselective catalyst, reacting with virtually all functional groups that have Lewis base properties.^{34,36} Zinc chloride (ZnCl₂), however, is a mild and selective catalyst in reactions where halides or alcohols are required to react selectively with an olefinic double bond.^{32,37} Tin tetrachloride (SnCl₄) is a very mild catalyst that can be used for acylation of reactive aromatic nuclei such as thiophene. Catalysis of reactions involving thiophene with $AlCl_3$ is too vigorous and extensive decomposition accompanies the process.^{32,38} Tin tetrachloride has also been applied to Friedel-Crafts reactions of active aromatics^{32,39} which cannot tolerate vigorous reaction conditions, as with furan derivatives for example.^{32,40} These few examples clearly demonstrate that a good working knowledge of the relative acid strength of Lewis acids is essential for understanding many important reactions in synthesis.

^{31.} Andrews, L.J.; Keefer, R.M. J. Am. Chem. Soc. 1952, 74, 4500.

^{32.} Olah, G.A., Friedel Crafts and Related Reactions, Vol. I, Interscience Publishers, 1963, New York, pp 201-366.

^{33. (}a) Inukai, T.; Kasai, M. J. Org. Chem. 1965, 30, 3567, (b) Inukai, T.; Kojima, T. Ibid 1967, 32, 869, 872.

For references dealing with coordination of the Lewis acid to ester dienophiles, see (a) Lappert, M.F. J. Chem. Soc. 1961, 817, (b) Lappert, M.F. Ibid 1962, 542.

 ⁽a) Houk, K.N.; Strozier, R.W. J. Am. Chem. Soc. 1973, 95, 4094, (b) Alston, P.V.; Ottenbrite, R.M. J. Org. Chem. 1975, 40, 1111, (c) Ansell, M.F.; Nash, B.W.; Wilson, D.A. J. Chem. Soc. 1963, 3012.

^{36.} Thomas, C.A. Anhydrous Aluminum Chloride in Organic Chemistry, Reinhold Publishers, New York, 1941.

^{37.} Nenitzescu, C.D.; Isa cescu, D.A. Berichte 1933, 66, 1100.

^{38.} Goldfarb, I. J. Russ. Phys. Chem. Soc. 1930, 62, 1073 [Chem. Abstr. 25: 2719, 1931].

^{39.} Stadnikoff, G.; Banyschewa, A. Berichte 1928, 61, 1996.

^{40.} Gilman, H.; Calloway, N.O. J. Am. Chem. Soc. 1933, 55, 4197.

2.4. HARD-SOFT ACID-BASE THEORY^{41,42}

2.4.A. Hard and Soft Acids and Bases

There is an alternative view of acid-base reactions that relies on the Lewis acid-base definition, but is used to classify a wide range of organic reaction types. Cations are classified as Lewis acids, anions are Lewis bases and salts are viewed as acid-base complexes. When one writes the normal acid-base equation, certain conventions are observed.

A' + A−B → A'−B + A

implies that A' is a stronger acid than A, and

 $B' + A-B \longrightarrow A-B' + B$

implies that B' is a stronger base than B. For

 $A + B \longrightarrow A-B$

where the equilibrium constant is defined by

 $\log K = [S_A] [S_B]$

where the *S* terms represent the relative strengths, which are functions of the environment and the temperature. There are solvent effects that make it difficult to establish a universal order of acid or base strength⁴³ due to variations in the parameter *S* as well as other factors.

For example, if the acid (A) is chromic acid there is a different basicity order than if A is cuprous ion. Usually, the simple equation shown above is inadequate and requires additional terms

$$\log K = [S_{A}][S_{B}] + [s_{A}][s_{B}]$$
 2.1

where *s* is a parameter for the strength of each acid and base, and is called the softness parameter.

The **Edward's equation**⁴⁴ (Eqn. 2.2) can be of value for determining the relative strength of Lewis acids and is written as

$$\log \frac{K}{K_0} = \alpha E_n + \beta H$$
 2.2

44. Edwards, J.O. J. Am. Chem. Soc. 1954, 76, 1540.

^{41. (}a) Pearson, R.G. *Hard and Soft Acids and Bases*, Dowden, Hutchinson and Roe Inc., Stroudsburg, PA, 1973;
(b) Pearson, R.G. *J. Am. Chem. Soc.* 1963, 85, 3533; (c) Pearson, R.G.; Songstad, J. *Ibid* 1967, 89, 1827; (d) *Idem J. Org. Chem.* 1967, 32, 2899.

^{42. (}a) Pearson, R.G. J. Chem. Educ. 1968, 45, 581; (b) Idem Ibid 1968, 45, 643.

 ⁽a) Lewis, G.N. Valence and the Structure of Atoms and Molecules, The Chemical Catalog Co., New York, 1923; (b) Lewis, G.N. J. Franklin Inst. 1938, 226, 293.

where H is a proton basicity factor: $H = 2.74 + pK_a$ for water, at 25°C. The term E_n is a redox factor and is equal to $E^\circ + 2.60 [E_n = E^\circ + 2.60]$, where E° is the standard oxidation potential for the base, defined by the reaction:

$$B^- \longrightarrow B^+ + 2e^-$$

There are obviously many acids, but the proton (H⁺) and an alkyl mercuric ion (RHg⁺) have roughly opposite affinities for binding bases. The values of the parameters for the Edward's equation for H⁺ are $\alpha = 0.000$ and $\beta = 2.000$ and for MeHg⁺ the values are $\alpha = 5.786$ and $\beta =$ -0.031.^{42,45} The reactions of these two acids with Lewis bases define the relative strengths of the Lewis bases, which gives rise to two observations. (*1*) Bases in which the donor atom is O, N, or F prefer to coordinate to the proton. (*2*) Bases in which the donor atom is P, S, I, Br, Cl, or C prefer to coordinate to mercury.

Table 2.5. Classification of hard and soft acids ^a

Hard acids	Borderline cases	Soft acids		
$\begin{array}{l} H^{+}, Li^{+}, Na^{+}, K^{+}, Mg^{2+}, Ca^{2+},\\ La^{3+}, Ce^{4+}, Gd^{3+}, Ti^{4+}, Cr^{3+},\\ Cr^{\Lambda+}, MoO^{3+}, Mn^{2+}, Mn^{7+},\\ Fe^{3+}, Co^{3+}, BF_3, BCl_3, B(OR)_3,\\ Al^{3+}, AlMe_3, AlCl_3, AlH_3,\\ CO_2, RCO^{+}, Sn^{4+}, Me_2Sn^{2+},\\ RPO_2^{+}, ROPO_2^{+}, SO_3, RSO_2^{++},\\ ROSO_2^{+}, HX (hydrogen bonding molecules), metal atoms, bulk metals \end{array}$	$\begin{array}{l} Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+},\\ Rh^{3+}, Ir^{3+}, Ru^{3+}, Os^{2+},\\ BMe_2, R_2C^+, C_6H_5^+, Sn^{2+},\\ Pb^{2+}, NO^+, Sb^{3+}, Bi^{3+}, SO_2 \end{array}$	Pd ²⁺ , Pt ²⁺ , Pt ⁴⁺ , Cu ⁺ , Ag ⁺ , Au ⁺ , Cd ²⁺ , Hg ⁺ , Hg ²⁺ , MeHg ⁺ , BH ₃ , Tl ⁺ , TlMe ₃ , CH ₂ , carbenes, \neq -acceptors, (chloronil, quinones, tetracyanoethylene, etc.), HO ⁺ , RO ⁺ , RS ⁺ , RSe ⁺ , Br ₂ , I ₂ , O, Cl, Br, I, N., RO, RO ₂ , M°		
^a In all cases, the molecules are listed in descending order (the first entry in each column is the hardest or softest).				
Reprinted with permission from Pearson, R.G. and the Journal of Chemical Eductation, Vol. 45, 1868 , 581-587. Copyright 1968, Divison of Chemical Education, Inc.				

In Group 1, the donor atoms are highly electronegative, have a low polarizability, and are hard to oxidize. These are called **HARD BASES** (valence electrons are bound tightly). In group 2, the donor atoms are of low electronegativity, are highly polarizable and are easy to oxidize.^{41c} These are called **SOFT BASES** (valence electrons are loosely bound).^{41c} Recognition of these categories forms the basis of the HSAB principle, initially developed by Pearson⁴¹ and also described by Ho.⁴⁵

In separate reactions with hard bases, there are two distinct classes of acids called **HARD ACIDS** and **SOFT ACIDS**. For **HARD ACIDS**,^{41c} acceptor atoms are small in size, have a high positive charge, and do not contain unshared pairs of electrons in their valence shell. They are of low polarizability and of high electronegativity. For **SOFT ACIDS**,^{41c} acceptor atoms are large in size, have a low positive charge, and contain unshared *p* or *d* electrons in the

^{45.} Ho, T.-L. Hard and Soft Acids and Bases Principles in Organic Chemistry, Academic Press, New York, 1977.

valence shell. They are highly polarizable and of low electronegativity.

In order to rank these acids according to their relative strength, the criteria of Schwarzenbach^{46a} and Ahrland and co-workers^{46b} were used. Hard acids form complexes with the following relative stability:⁴⁵

Ν	>>	Р	>	As	>	Sb
0	>>	S	>	Se	>	Te
F	>	Cl	>	Br	>	Ι

Similarly, soft acids react in the following manner to produce stable complexes:45

N	<<	Р	>	As	>	Sb
0	<<	S	<	Se	<	Te
F	<	Cl	<	Br	<	Ι

A list of commonly used hard and soft acids is shown in Table 2.5. 42a,47 Lewis acids with large α and β values tend to be soft, and Lewis acids with small α and β values are hard. Soft acids form stable complexes with bases that are highly polarizable and good reducing agents (not necessarily good bases toward the proton). Hard acids usually form stable complexes with bases that are good bases toward the proton. A comparison of the ability of Lewis acids to bind donating atoms of Lewis bases is conveniently made by examining the order of the donor atoms as a function of increasing electronegativity:

As,
$$P < C$$
, Se, S, $I < Br < N$, $Cl < O < F$

where the atoms on the left form more stable complexes with soft Lewis acids, and those on the right form more stable complexes with hard Lewis acids.

In general, hard acids prefer to bind to hard bases and soft acids prefer to bind to soft bases. Several other general comments can be made.

1. Heavier and less electronegative members of a series are usually softer.

$$\begin{array}{rrrr} R_3P &>& R_3N \\ (\text{softer}) & I^- &>& Br^- &>& CI^- &>& F^- \mbox{ (harder)} \end{array}$$

2. The more p character, the softer the acid.

(softer)
$$sp^{3}C > sp^{2}C > spC$$
 (harder)

3. The more electron releasing groups on the moiety, the harder the acid.

(harder) $(CH_3)_3C \oplus > (CH_3)_2HC \oplus > (CH_3)H_2C \oplus > H_3C \oplus (softer)$

 ⁽a) Schwarzenbach, G. *Experientia Suppl.* 1956, 5, 162 [*Chem. Abstr.* 51:7293a 1957]; (b) Ahrland, S.; Chatt, J.; Davies, N.R. *Quart. Rev. (London)* 1958, 12, 265.

^{47.} Reference 45, p 5.

Metals require a minimum of a half-filled outer d shell to be good acceptors,⁴⁸ emphasizing the importance of *d* electrons for metal ions. A comparison of the series Ca \rightarrow Zn suggests that their ions should become harder due to increasing nuclear charge. One also expects an increase in electronegativity, and therefore an increase in hardness. In fact, the increase in d electrons leads to increasing softness in this series.

The softness of a base is defined by the equilibrium established in the reaction of MeHg⁺ and BH⁺:

$$MeHg^{+}_{(aq)} + BH^{+}_{(aq)} \xrightarrow{K} MeHgB^{+}_{(aq)} + H^{+}_{(aq)}$$

If *K* is much greater than one, the base is soft. Conversely, if $K ext{ is } \le 1$, the base is hard. Table 2.6 shows common hard and soft bases.^{47,42a,49} The nature of the outer groups on the acceptor atom is important. The hard acid BF₃ possesses hard fluoride ions and readily adds to hard bases. This contrasts with BH₃, which is a soft acid, where soft hydride ions readily add to soft anions. Soft bases tend to group together on a given central atom as do hard ligands. There is a mutual stabilizing effect called **symbiosis**.⁵⁰

Table 2.6. Classification of Hard and Soft Bases^a

Hard acids	Borderline cases	Soft acids		
$\label{eq:2.1} \begin{array}{l} NH_3, RNH_2, N_2H_4, H_2O, ^OH,\\ O^{2-}, ROH, RO^-, R_2O, AcO^-,\\ CO_3^{2-}, NO_3^-, PO_4^{3-}, SO_4^{2-},\\ CIO_4^-, F^-(CI^-) \end{array}$	$C_6H_5NH_2, C_5H_5N, N_3^-, N_2, NO^{2-}, SO_2^{2-}, Br^-, R_2S, RSH, RS^-, S_2O_3^{2-}, I^-$	H ⁻ , R ⁻ , CH ₂ =CH ₂ , C ₆ H ₆ , CN ⁻ , RNC, CO, SCN ⁻ , R ₃ P, (RO) ₃ P		
^a In all cases, the molecules are listed in descending order (the first entry in each column is the hardest or softest).				
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In the case under consideration, the hard fluoride ligands form a complex that makes boron essentially 'B⁺' and hard. The soft hydride donates negative charge to the central boron by via a covalent bond, or by simple polarization, making the boron more neutral and soft. It appears that the actual charge on the central atom, rather than the formal charge, determines the degree of softness. Pearson pointed out "while the HSAB principle has proved useful in many ways,^{41a} it has been justifiably criticized because of the lack of a precise definition of hardness and the inability to assign numbers to this property".⁵¹ The hardness parameter (η) is now defined in terms of electronegativity as in Equation 2.3⁵²

^{48.} Ahrland S. Structure and Bonding, 1966, 1, 207.

^{49.} Reference 45, p 6.

^{50.} Jorgensen, C.K. Structure and Bonding (Berlin) 1966, 1, 234.

^{51.} Pearson, R.G. J. Chem. Educ. 1987, 64, 561.

^{52.} Parr, R.G.; Pearson, R.G. J. Am. Chem. Soc. 1983, 105, 7512.

$$\eta = \frac{1}{2} \frac{\partial^2 E}{\partial N^2} = \frac{1}{2} \frac{\partial M}{\partial N}$$
 2.3

where ∂E and ∂N are obtained from the Mulliken electronegativity (χ_M) .⁵³ Pearson used an operational definition of hardness (Equation 2.4).

$$\eta = \frac{I - A}{2} \qquad 2.4$$

In this definition, *I* is the ionization potential and *A* is the electron affinity. It was noted that a hard molecule will have a large value of η . For a reaction A + B \rightarrow A:B, the following expression can be used to decide which is the acid, A or B:⁵¹

$$(I_A - A_B) - (I_B - A_A) = 2 (X^{\circ}_A - X^{\circ}_B)$$
2.5

If this quantity is positive, transferring an electron from B to A requires less energy than from A to B. The A group is then a Lewis acid. The direction of electron flow can be determined by the difference in absolute electronegativities, whose magnitude is a measure of the driving force for the transfer.⁵¹

In most cases, there will be electron transfer in both directions. Equation 2.6 gives the total energy when the amount of electron transfer in both directions is near unity (~ 1).

$$(I_A - A_B) + (I_B - I_A) = 2 (\eta_A - \eta_B)$$
26

If both A and B are hard, then η_A and η_B will be large, and transfer of electrons in *both* directions will be disfavored. If A and B are soft, however, η_A and η_B will be small, favoring electron transfer.⁵¹ Table 2.7⁵¹ provides typical values for electronegativity (X°) and for hardness (η) for several cations, anions and neutrals.

From Table 2.7, it is apparent that Al^{3+} ($\eta = 45.8 \text{ eV}$) is a hard Lewis acid, whereas Ag^+ ($\eta = 6.9 \text{ eV}$) is a soft Lewis acid. To illustrate neutral molecules, hydrogen (H₂) is harder than iodine (I₂), and chloromethane ($\eta = 7.5 \text{ eV}$) is harder than iodomethane ($\eta = 4.7 \text{ eV}$). Trimethylamine ($\eta = 6.3$) is a harder base than trimethylphosphine ($\eta = 5.9$).

^{53.} Mulliken, R.S. J. Chem. Phys. 1934, 2, 782.

Ion/Molecule	X° (eV)	η (eV)	Ion/Molecule	X° (eV)	η (eV)
N7 +	26.2	01.1	- 21	22.4	
Na'	26.2	21.1	Fe ²⁺	23.4	7.3
Agʻ	14.6	6.9	Zn^{2+}	28.8	10.8
I ⁺	14.8	4.3	Pd ²⁺	26.2	6.8
Mn^{2+}	24.4	9.3	Hg ²⁺	26.5	/./
Ca ²⁺	31.6	19.7	Al^{J^+}	/4.2	45.8
		NEU	TRALS		
BF ₃	7.8	7.8	C_4H_5N	4.4	6.0
SO3	7.2	5.5		4.4	6.1
N_2	7.0	8.6	H_2S	4.3	6.4
Cl ₂	7.0	4.6	C ₆ H ₆	4.0	5.2
SO ₂	6.7	5.6	PH ₃	4.0	6.0
H ₂	6.7	8.7	H ₂ O	3.1	9.5
O ₂	6.3	5.9	MeCl	3.8	7.5
СО	6.1	7.9	NH ₃	2.9	7.9
I ₂	6.0	3.4	PMe ₃	2.8	5.9
Pt	5.6	3.5	Me ₂ S	2.7	6.0
MeI	4.9	4.7	Me ₂ O	2.0	8.0
HCl	4.7	8.0	NMe ₃	1.5	6.3
F^-	3.40	7.0	Br ⁻	3.36	4.2
HO ⁻	1.83	5.7	I ⁻	3.06	3.7
H_2N^-	0.74	5.3	H^-	0.74	6.8
H_3C^-	0.08	4.9	MeS ⁻	1.9	3.1
Cl ⁻	3.62	4.7	t-Bu ⁻	-0.3	3.6
HS ⁻	2.30	4.1	$C_6H_5^-$	1.1	4.1
H_2P^-	1.25	4.3	NO_2^-	3.1	3.9
[Reprinted with permission from Parr, R.G.; Pearson, R.G., J. Am. Chem. Soc., 1983, 105, 7512. Copyright © 1983 American Chemical Society.]					

Table 2.7. Electronegativity and Hardness Parameters

2.4.B. HSAB and Molecular Orbital Theory

Frontier molecular orbital (FMO) theory (sec. 11.2) correlates molecular orbital energies and orbital coefficients with the relative reactivity of molecules. In a molecule, the orbital containing the highest energy bonding electrons is called the highest occupied molecular orbital (HOMO) and the lowest lying orbital that does not contain electrons but can receive them is the lowest unoccupied molecular orbital (LUMO). Both HOMO and LUMO are shown in Figure $2.1.^{51}$ The difference in energy between these orbitals determines the reactivity of many types of reactions. Experimentally, the energy of the HOMO is the ionization potential (*I*) and the energy of the LUMO is the electron affinity (*A*), leading to the equations:

$$I = -\varepsilon_{HOMO}$$
 and $A = -\varepsilon_{LUMO}$

In Figure 2.1, the electronegativity (X°) is taken as the midpoint (average) between the HOMO and LUMO energies.⁵¹ If the HOMO is -10 eV and the LUMO is +1 eV, then the midpoint is

5.5 eV and the value of X° is 1 eV –5.5 eV = –4.5 eV. The parameter η will then be 5.5 eV (see Fig. 2.1), which allows one to define a hard molecule or ion as having a large energy gap between the HOMO and LUMO ($\Delta_{HOMO-LUMO}$).⁵¹ A soft molecule or ion will have a small $\Delta_{HOMO-LUMO}$.⁵¹ Soft acids and bases have properties that lead to a high energy HOMO and a low energy LUMO (a small energy gap). Hard acids and bases have the opposite properties: a low energy HOMO and a high-energy LUMO (a large energy gap). This generalization can be applied to cations, anions and radicals as well as neutral molecules. Radicals contain a singly occupied molecular orbital (SOMO) as shown in Figure 2.2.⁵¹ The electron affinity term in this case arises from adding a second electron to the SOMO and X° is the average energy of the two electrons.⁵⁴



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Figure 2.2. Energy Diagram for Radicals

The HOMO-LUMO energy gap is usually the lowest energy electron absorption band. Soft acids and bases tend to absorb light closer to the visible region than do hard acids and bases. Alkenes are chromophoric and it is typical for them to have high-energy HOMOs and low energy LUMOs. In general, unsaturation increases softness. It is also apparent that soft molecules are more reactive than hard molecules (due to a smaller energy gap I-A) in unimolecular and bimolecular reactions.

These principles finally allowed Pearson to define hardness (η) as follows:⁵¹ a hard molecule resists changes in its electron charge cloud, both the total amount of charge and the charge distribution in space. A soft molecule has an easily changed electron distribution.

2.4.C. Applications of HSAB Theory

HSAB theory has been applied to many chemical reactions not usually classified as acid-base

54. Klopman, G. J. Am. Chem. Soc. 1964, 86, 1463.

reactions. Careshould be exercised in nontrivial cases, but this approach may be of value in predicting the likelihood of a number of reactions in a synthetic plan. Several examples are illustrated below.⁵¹

2.4.C.i. Substitution (also see sec. 2.6). Saville showed that nucleophilic displacement of alkyl halides can be characterized by HSAB theory.⁵⁵ In general, the reaction works best when the R group and nucleophile partner are matched. The two major categories are



When R–C has a greater differential in hardness and softness, the reaction proceeds best. Table 2.7 shows that chloromethane is harder than iodomethane. Therefore, a hard base such as methoxide will show a larger energy difference for iodomethane, and should react faster.

2.4.C.ii. E2 versus $S_N 2$ (see secs. 2.9.A and 2.6.A). Ethoxide and the malonate anion are about equal in basicity,⁵⁶ but ethoxide is a much harder base. Reaction of 2-bromopropane with ethoxide gives primarily elimination, but similar reaction with the malonate anion gives the substitution product 27. In general, hard bases give elimination and soft bases give substitution, but the gegenion has a profound influence on the course of the reaction. Reaction of 1-bromo-2-chloroethane with 28 gave only elimination (to bromoethene or chloroethene), leaving behind the neutral substrate 29. However, reaction with chloromagnesium salt 30 gave nucleophilic displacement with formation of 31 after a second displacement by the enamine (sec. 9.6) formed in the first substitution.⁵⁷



^{55.} Saville, B. Angew. Chem. Int. Ed. 1967, 6, 928.

^{56.} Pearson, R.G.; J. Am. Chem. Soc. 1949, 71, 2212.

^{57. (}a) Evans, D.A.; Bryan, C.A.; Wahl, G.M. J. Org. Chem. 1970, 35, 4122; (b) Reference 44, pp 56-57.

2.4.C.iii. Epoxidation. Peroxyacids such as **32** (sec. 3.4.C) contain an unusual soft-hard combination that leads to attack by an alkene (a soft base) on the soft oxygen of the peroxyacid.

$$\underset{32}{\overset{O}{\overset{S}}_{H}} \overset{S}{\underset{H}{\overset{O}{\overset{O}{\overset{O}{\overset{C}}}}}} H \xrightarrow{\overset{S}{\overset{CH_{2}=CH_{2}}{\overset{O}{\overset{O}{\overset{O}{\overset{C}}}}}} \overset{O}{\underset{H}{\overset{O}{\overset{C}}} + \underset{R}{\overset{O}{\overset{O}{\overset{O}{\overset{C}}}} H \xrightarrow{O} H$$

2.4.C.iv. Carbonyls. The carbon of a carbonyl is a hard acceptor and the oxygen is a hard donor.

Hard acceptor \implies C \equiv O \iff Hard donor

An example is **33**, which reacts with the soft thiophenoxide (PhS⁻) at the tosylate center (C-OTs) to give **34**.⁵⁸ Reaction of **33** with the harder cyanide ion, however, gives **35** and subsequent ring closure, where the alkoxide unit displaces tosylate to generate oxetane **36**.⁵⁸ Thiophenoxide is a soft base that reacts with the soft acid (CH₂OTs),



whereas cyanide is a hard base that reacts with the hard acid (the carbonyl). Reductive hydrogenolysis of α -bromoketones (**37**) by some metal borohydrides (not NaBH₄, see sec. 4.4.A) is another example. Transfer of the soft base (hydride) leads to loss of the halide (a soft base). The reaction works best when the metal (M⁺) is a soft acid.⁵⁹ The sodium counterion in sodium borohydride is a hard acid and does not work well in this reaction. A soft acid such as copper or lead, however, will facilitate the reduction.^{60,61} Reduction with metal borohydrides will be discussed in section 4.4.B.

Conjugate reduction of α , β -unsaturated ketones (sec. 4.2-4.5) can also be explained by HSAB theory.⁶² The β -carbon of a conjugated ketone (**38**) is softer than the carbonyl. A covalent M-H reagent such as hydride is soft and LiAlH₄ reduction of cyclohexenone gave 22% of

^{58. (}a) Nerdel, F.; Weyerstahl, P.; Lucas, K. Tetrahedron Lett. 1968, 5751; (b) Reference 44, p 86.

^{59.} Reference 45, p 92.

^{60.} Goto, T.; Kishi, Y. Tetrahedron Lett. 1961, 513.

^{61.} Goto, T.; Kishi, Y. Nippon Kagaku Zasshi 1962, 83, 1135 [Chem. Abstr. 58: 14059a, 1963].

^{62.} Bottin, J.; Eisenstein, O.; Minot, C.; Anh, N.T. Tetrahedron Lett. 1972, 3015.

the conjugate reduction product. Conversely, lithium trimethoxyaluminum hydride (sec. 4.3) suppresses the soft conjugate addition since the alkoxy groups are hard and only 5% of conjugate addition was observed with this reagent.⁶³ The presence of an alkyl group increases the softness of the borohydride. Sodium borohydride gives mainly 1,2-addition but potassium tri-*sec*-butylborohydride (K-Selectride, sec. 4.5.C) gives mainly 1,4-reduction.⁶⁴ The B-H bond is more covalent than Al-H, and borohydrides are softer than aluminum hydrides, and this accounts for the observation that BH_4^- is relatively inert to the hard acid H⁺. Softer cations such as Na⁺ favor 1,4-reduction and it is known that NaBH₄ gives more 1,4-reduction than LiBH₄.⁶⁵

The reaction of enones with organometallics also follows this pattern. Dialkylcuprates (with a soft copper) are soft and give primarily 1,4-addition. When organolithium reagents (with a hard Li atom) react with enones, the major product is 1,2-addition. The hardness of common organometallics follows the order:⁶⁶

The alkyl portion also plays an important role. The hardness order of alkyl fragments is:66

(harder) Me > Et > *i*-Pr > *t*-Bu (softer)

This reactivity order suggests that *tert*-butylmagnesium halides are softer and will give more conjugate addition than methylmagnesium halides.^{67,66} When the alkyl fragment of an organocuprate is hard (such as lithium trialkynyl cuprates) the reagent adds to the carbonyl via 1,2-addition.⁶⁸



2.4.C.v. Enolate Anions. Enolate anions such as **39** are bidentate nucleophiles (the carbanion and alkoxy units can both donate electrons) and bidentate bases. Oxygen is a harder base than carbon and reaction with hard acids tends to give more *O*-alkylation. The hardness of alkyl halides is RCl > RBr > RI, and more C alkylation is expected with R-I, but more O alkylation with R-Cl.⁴² The product distribution varies as the polarity of the solvent is changed, however.⁴² In general, acylation and silylation of enolates (classified as hard acids) give more *O*-substituted product. The ease of C-X bond cleavage parallels the softness of X. In general, the hard Si atoms tend to form strong bonds with oxygenated compounds.

^{63.} Durand, J.; Anh, N.T.; Huet, J. Tetrahedron Lett. 1974, 2397.

^{64.} Ganem, B. J. Org. Chem. 1975, 40, 146.

^{65.} Wheeler, J.W.; Chung, R.H. J. Org. Chem. 1969, 34, 1149.

^{66.} Reference 45, p 94.

^{67.} Damiano, J.C.; Diara, A. C.R. Hebd. Seances Acad. Sci. Ser. C 1973, 276, 441.

^{68.} Palmisano, G.; Pellegata, R. J. Chem. Soc. Chem. Commun. 1975, 892.

2.4.C.vi. Hydroboration

acceptor \implies B-H \iff soft base (H⁻)

The reaction between alkenes and boranes forms the basis of hydroboration (see Chap. 5). Borane (B_2H_6 , formally known as diborane) is a soft Lewis acid and will complex with soft bases such as alkenes. When BH_3



(the monomeric form of diborane) reacted with a vinyl chloride, the boron was attached primarily to the α -carbon (**40** gave 60% of **41** and 40% of **42**).⁶⁹ Reaction with enol ether **43**, however, gave only **44**.⁶⁹ Both chlorine and ethoxy are hard bases and influence hardness at the *ipso*-carbon.⁷⁰ Ethoxy is harder and accounts for the predominance of **44**. The chlorine substituent leads to resonance stabilization that swamps the increase in hardness. The increased regioselectivity observed in reactions of chloroborane, for example (ClBH₂, sec. 5.2.A), is attributed to the heightened hardness of the boron atom,⁷¹ induced by the chlorine.

2.5. ACYL ADDITION, SUBSTITUTION AND CONJUGATE ADDITION

In general, nucleophiles react with ketones and aldehydes at the acyl carbon (the carbonyl carbon), breaking the π bond and forming a new bond to carbon. This class of organic reactions is called nucleophilic acyl addition. When the carbonyl contains a leaving group, acyl addition is followed by loss of that group to give a substitution product, and the overall process is called acyl substitution. Conjugate carbonyl compounds have a C=C unit attached to the carbonyl, and the π -bond extends the reactivity: ${}^{b}C = \tilde{C} - \tilde{C} = O^{b}$. In other words, the nucleophile can react with the C=C unit as well as the C=O unit. This extension of reactivity by conjugation to a π -bond is called **vinylogy**. A nucleophile can, therefore, attack the C=C unit in the conjugated system in what is called conjugate addition or Michael addition. All of these types of reactions will be discussed.

2.5.A. Nucleophilic Attack

The discussion of Lewis acids made it clear that electrophilic centers other than a proton can

71. Reference 45, p 157.

^{69. (}a) Brown, H.C.; Sharp, R.L.J. Am. Chem. Soc. 1968, 90, 2915; (b) Pasto, D.J.; Snyder, R. J. Org. Chem. 1966, 31, 2773.

^{70.} Reference 45, p 156.

react with an electron-donating species. Bond polarization, induced by the presence of more electronegative atoms, will polarize atoms that are connected to the electronegative atom by covalent bonds. If the bond polarization leads to a δ + dipole on an atom, that atom can react with reagents that donate electrons. A simple example is the reaction of carbonyls (C=O) with the nucleophilic alkyne anion. The carbonyl carbon has a positive dipole ($^{\delta+}C$) because of the electronegative oxygen atom, and that carbon can accept an electron pair (it is termed an electrophile or electron loving) from the negatively charged carbon of MeC=C: $^{-}$ to give 45. The halogen-bearing carbon of an alkyl halide also has a positive dipole that makes it electrophilic, and attack by the carbanionic carbon will lead to displacement of the iodide (to form 46) in a S_N2 reaction, which will be discussed in sec. 2.6.A. Formation of both 45 and 46 are reasonable extensions of Lewis acid-Lewis base reactions, but the electrophilic center is a carbon atom in both cases. Although the attacking species is formally a Lewis base, it is convenient to designate it as a **nucleophile** (nucleus loving) to emphasize its attack on carbon rather than other electrophilic atoms. A nucleophile is therefore defined as a species able to donate two electrons to carbon, forming a new bond to that carbon. As we will see in section 2.9.A., if a nucleophile is a relatively strong base as well as a nucleophile, elimination can compete with substitution.



The reactivity of a nucleophile reacts with an electrophile depends on both the strength of the nucleophile (its ability to donate electrons to carbon) and the nature of the carbonyl substrate. An order of nucleophilic strength for reaction of different nucleophiles *with a carbonyl* is⁷²

 $C=N-O^- > EtO^- > MeO^- > HO^- > N_3^- > F^- > HOH > Br^- > I^-$

It is important to mention that nucleophilic strength for a given nucleophile changes with the electrophile. In other words, the nucleophilic alkyne anion from above will exhibit different nucleophilic strength with a ketone than with an alkylhalide. A complete discussion of nucleophilic

strength will be delayed until sec. 2.7.A, in connection with reactions of nucleophiles and alkyl halides.⁷³ This section will focus on nucleophilic reactions of carbonyl compounds. There are three fundamental types of reactions: (1) acyl addition, (2) acyl substitution, and (3) conjugate addition when the carbonyl is conjugated to a π bond. As mentioned above, inductive effects make the β -carbon of the π bond electrophilic (see 47) and subject to nucleophilic attack.



^{72.} Koskikallio, J. Acta Chem. Scand. 1969, 23, 1477, 1490.

^{73.} Harris, J.C.; Kurz, J.L. J. Am. Chem. Soc. 1970, 92, 349.

2.5.B. Acyl Addition to Carbonyls⁷⁴

Nucleophilic addition to a carbonyl can be reversible if the attacking nucleophilic species becomes a good leaving group in the product (leaving groups are discussed in sec. 2.7.E). Water and hydroxide, for example, add reversibly. When water adds to cyclohexanone, the product is **48**, but H₂O is a good leaving group in the presence of the alkoxide unit, making the reaction reversible as shown. As a practical matter, such reversibility occurs when weak nucleophiles react with aldehydes and ketones. The process becomes effectively irreversible if the nucleophile becomes a poor leaving group in the product. When Na^{+–}C=CMe reacts with a carbonyl a carbon-carbon bond is formed which is a very poor leaving group for the reverse reaction, making the reverse reaction difficult. For this reason, cyclohexanone reacts with the sodium salt of 1-propyne to give alkoxide **49**. Acetylides such as –C=CMe add to carbonyls and the C–C=C unit is a very poor leaving group so the addition is essentially irreversible. A hydrolysis step generates the final alcohol product, **50**. Clearly, this analysis is overly simplistic and the nucleophilic strength of the incoming reagent as well as the groups attached to the acyl carbon play a major role. This analysis does illustrate the important role played by the nucleophile and the nature of the product that results from acyl addition.



As with water, ethanol or other alcohols are weak nucleophiles and acyl addition to cyclohexanone is reversible. One method to improve the reaction is to protonate the acyl unit of cyclohexanone to give an oxygen-stabilized carbocation by adding an acid catalyst. Protonation of cyclohexanone, for example, gives resonance stabilized cation 51 (sec. 2.6.B.i and 12.2) that reacts with ethanol to give 52. Loss of a proton regenerates the acid catalysts and forms hemi-acetal 53. All steps are reversible, but in the presence of the acid catalyst and ethanol solvent (i.e., a large excess of ethanol), the equilibrium favors formation of the hemiketal. Subsequent protonation of OH, loss of water, addition of a second molecule of ethanol, and loss of a proton gives the diethyl ketal of cyclohexanone (1,1-diethoxycyclohexane, 54). Aldehydes react with alcohols to give acetals. Ketals and acetals are common protecting groups for the carbonyl group (sec. 7.3.B.i). When thiols are used in this reaction, dithioketals or dithioacetals are formed. Primary amines react to give imines and secondary amines react to give enamines (sec. 9.6). Although acyl addition is usually reversible, addition of excess reagent (such as ethanol) or removal of a product (water) will drive the equilibrium from ketone to ketal (or another addition product). Conversely, if the ketal is treated with an acid catalyst in the presence of excess water (aqueous acid for example), the equilibrium will shift

^{74.} For examples see reference 3, pp 1125-1188.

to favor the ketone. In other words, the ketal will be hydrolyzed to the ketone.



In general, addition of carbon nucleophiles to a carbonyl is irreversible (or the equilibrium greatly favors the product) and addition of heteroatom nucleophiles is reversible. Even when the reaction equilibrates, the equilibrium may lie to the side of the products. Heteroatom nucleophiles often require an acid catalyst in order to establish an equilibrium that leads to good yields of acyl addition products. All of these reactions are discussed in any undergraduate Organic chemistry book so we will keep the focus on addition of strong nucleophiles.

2.5.C. Acyl Substitution of Carbonyl Compounds⁷⁵

Derivatives of carboxylic acids such as acid chlorides and esters have an interesting structural feature when compared to a ketone or an aldehyde. The carbonyl carbon of these groups bear a chlorine or an OR group, respectively. When a nucleophile adds to the carbonyl the resulting alkoxide intermediate, called a **tetrahedral intermediate** bears the Cl or OR units, which are putative leaving groups. If the newly formed bond is rather strong, such as a C–C bond, both the C–Cl or C–OR bonds are relatively easy to break. Regeneration of the C=O unit is accompanied by loss of Cl⁻ or RO⁻, which are rather stable ionic entities, and the overall result of this process is a substitution reaction where the nucleophile replaces chlorine on the carbonyl. This reaction with carboxylic acid derivatives (acid chlorides, esters, anhydrides, amides) is called **acyl substitution**. Many types of nucleophiles can be used, including hydroxide, alkoxides or amines in addition to carbon nucleophiles (see chap. 8). Acyl addition of hydroxide ion to benzoyl chloride, for example, gives **55** as the initial product. It is a reactive intermediate and loss of the chloride ion leads to benzoic acid. Under these basic conditions, the initially formed acid is converted to the carboxylate anion, requiring a neutralization step to recover the acid.



With ketones and aldehydes, addition of an anionic nucleophile leads to a species such as 48

^{75.} For examples see reference 3, pp 1717-1808, 1929-1994.

or 49, where there are strong C–C or C–H bonds, and the H or C units are not considered to be leaving groups. The presence of a leaving group in acid derivatives leads to this fundamental difference in reactivity between acyl addition and acyl substitution. This reaction is the basis of the acid catalyzed reaction of an alcohol with a carboxylic acid to give an ester. Note that a very effective method for the conversion of a carboxylic acid to a methyl ester is the reaction with diazomethane (CH₂N₂, see sec. 13.9.C). Acyl substitution also forms the basis for conversion of a carboxylic acid to an acid chloride with thionyl chloride, for conversion of an ester to an amide by reaction with an amine, and the acid or base hydrolysis of esters, acid chlorides, anhydrides, or amides to give carboxylic acids. Acyl addition can be reversible when the leaving group ability of the acyl derivative is close to that of the new nucleophile, as in the transesterification reaction of ethyl butanoate and methanol. The acid-catalyzed reaction of ethyl butanoate and methanol generates a tetrahedral intermediate bearing both OMe and OEt. and the equilibrium is driven to the methyl ester only if a large excess of methanol is present. Recognizing the mechanistic details of this process allows one to control the reaction, making a process like transesterification useful in synthesis. In a synthesis of (+)-aldosterone by Shea and co-workers,⁷⁶ methyl ester **56** was transesterified⁷⁷ with the chiral dimethyl-*tert*-butylsilylprotected (S,S)-hydrobenzoin 57 to give ester 58 in 75% yield and >99% ee. Formation of 58 allowed Shea to proceed with an asymmetric synthesis.



Nucleophilic addition of Grignard reagents to carboxylic acid derivatives is another example where acyl addition gives a product that can react with the reagent.⁷⁸ Initial addition to the carbonyl of methyl butanoate gives the tetrahedral intermediate **59**, which loses methoxide to give the ketone, 1-phenyl-1-butanone (**60**). Phenylmagnesium bromide reacts with the ketone faster than it does with the ester, however, to give **61**. Hydrolysis generates tertiary alcohol **62** (sec. 8.4.C.i).



^{76.} Bear, B.R.; Parnes, J.S.; Shea, K.J. Org. Lett. 2003, 5, 1613.

^{77.} Meth-Cohn, O. J. Chem. Soc. Chem. Commun. 1986, 695.

Kharasch, M.S.; Reinmuth, O. Grignard Reactions of Nonmetallic Substances, Prentice-Hall, Inc., Englewood Cliffs, New Jersey, 1954, pp 549-766, 846-869.

Esters, anhydrides, and amides give similar products via acyl substitution, followed by acyl addition to the initially formed product. The best leaving group is chloride followed closely by carboxylate (acid chlorides and anhydrides, respectively) and then the alkoxy group from an ester. Amides have a -NR₂ leaving group and are the least reactive. Therefore, acid chlorides and anhydrides should react with Grignard reagents to give a higher percentage of alcohol, whereas an ester might give a mixture of ketone and alcohol products. For the most part this is correct, but the product distribution depends on the reactivity of the Grignard reagent, the nature of the acid derivative, the solvent and temperature of the reaction. A useful approximation correlates the reactivity of the carbonyl moiety with the leaving group propensity of the ligand attached to carbon. This leads to the usual order of reactivity to nucleophilic acyl substitution as:

If a large excess of the nucleophile (such as excess Grignard) is used, most reactions are driven to give the tertiary alcohol as the major (often the only) product. In later chapters, the problem of reactivity of the ketone product with the organometallic reagents will be circumvented by use of a dialkyl cadmium reagent (sec. 8.4.C.ii).⁷⁹ The reaction of acid chlorides with organocuprates also gives the ketone in good yield (sec. 8.7). In some cases, functionalized amides can give good yields of the acyl addition product. A *N*-Methoxy-*N*-methyl amide such as **63** is referred to as a **Weinreb amide**.⁸⁰ In a synthesis of pumiliotoxins 209F and 251D,⁸¹ Jamison and Woodin reacted **63** with methylmagnesium bromide, and obtained an 94% yield of ketone **64** (note that the allylic carbamate unit is referred to as *N*-Alloc). Grignard reactions will be discussed further in section 8.4.C.ii.



2.5.D. Conjugate Addition⁸²

Conjugated ketones, aldehydes, esters and related molecules have a carbonyl unit connected directly to the π bond of an alkene (as in 65). Inductive effects make the terminal carbon of the alkene electrophilic, and subject to attack by a nucleophile in what is formally a vinylogous

^{79. (}a) Jones, P.R.; Desio, P.J. Chem. Rev. 1978, 78, 491; (b) Cason, J.; Fessenden, R. J. Org. Chem. 1960, 25, 477.

 ⁽a) Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* 1981, 22, 3815; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, p. 866.

^{81.} Woodin, K.S.; Jamison, T.F. J. Org. Chem. 2007, 72, 7451.

^{82.} For examples see reference 3, pp 1567-1616, 1809-1842.

acyl addition. This type of reaction is referred to as **conjugate addition** or **Michael addition**⁸³ (sec. 9.7.A) and it is facilitated by formation of a resonance-stabilized product, the enolate anion (**66**). Hydrolysis gives the final addition product, ketone **67**. Conjugate addition competes with normal nucleophilic attack at the acyl carbon (acyl addition), and the major product is usually determined by steric hindrance at the carbonyl or at the alkene carbon, and by the nature of the nucleophile. When the R group in **65** is hindered, attack at the acyl carbon can be difficult, leading to conjugate addition. When R is small, such as the H in conjugate aldehydes, normal 1,2-addition to the carbonyl (acyl addition) is usually preferred. Acyl addition is usually preferred with conjugated aldehydes with nucleophiles such as alkyne anions and Grignard reagents, but organocuprates give conjugate addition with conjugated aldehydes and with most α,β -unsaturated carbonyl derivatives (sec. 8.7.A.vi).^{84,85}



Conjugate addition will be a key feature of the **Robinson annulation**^{86,83} in sec. 9.7.C, in which a ketone enolate reacts with a conjugated ketone to give a cyclohexenone derivative. Michael additions are common in synthesis and we will discuss examples in chapter 8 and 9.

2.6. SUBSTITUTION REACTIONS

Replacement of one atom or functional group for another is referred to as substitution. The two major types of substitution previously discussed involve reaction at an sp³ carbon (nucleophilic aliphatic substitution) or at sp² carbonyl carbon (nucleophilic acyl substitution). Substitution reactions at an sp³ carbon can be mechanistically categorized as bimolecular or unimolecular. Bimolecular substitution formally refers to the fact that it follows second-order kinetics, but as a practical matter these reactions usually involve collision of a nucleophile with a carbon bearing a leaving group. Unimolecular substitution is again derived from the rate expression because the reaction follows first-order kinetics, but ionization of a substrate bearing a leaving group to form a carbocation intermediate is the rate-determining step, and this is followed by reaction with a nucleophile. The former reaction is labeled $S_N 2$ and the latter is labeled $S_N 1$.

^{83.} Bergmann, D.; Ginsburg, D.; Pappo, R. Org. Reactions, 1959, 10, 179.

^{84. (}a) Posner, G.H. An Introduction to Synthesis Using Organocopper Reagents, Wiley-Interscience, New York, 1980, (b) Mandeville, W.H.; Whitesides, G.M. J. Org. Chem. 1974, 39, 400, (c) House, H.O.; Wilkins, J.M. Ibid 1978, 43, 2443, (d) Whitesides, G.M.; San Filippo, Jr. J.; Casey, Jr., C.P.; Panek, E.J. J. Am. Chem. Soc. 1967, 89, 5302.

^{85. (}a) Davis, R.; Untch, K.G., J. Org. Chem. 1979, 44, 3755; (b) Stork, G.; Isobe, M. J. Am. Chem. Soc. 1975, 97, 6260, 4745.

^{86.} duFeu, E.C.; McQuillin, F.J.; Robinson, R. J. Chem. Soc. 1937, 53.

Both $S_N 2$ and $S_N 1$ reactions are extremely useful for the introduction of heteroatom and carbon functional groups into a carbon skeleton.

2.6.A. Aliphatic Bimolecular Nucleophilic Substitution

When a nucleophile collides with a sp³ carbon that is part of a polarized bond bearing a leaving group (an electrophilic carbon), it leads to the transform:

$$-C - Nuc \longrightarrow -C - X$$

and the experimental reaction required to accomplish this transform is

Nuc:
$$+ -C - X \longrightarrow Nuc - C + X$$

where X is a suitable leaving group and the reaction is called **nucleophilic aliphatic** substitution.⁸⁷

2.6.A.i. The $S_N 2$ Reaction. In reactions where the substrate (see 68) has a leaving group (X) connected to a sp³ carbon, displacement by a nucleophile leads to a product in which X has been replaced by the nucleophile to give 70. This process can be described as a bimolecular (it follows second order rate equation) substitution that involves a nucleophile and the mechanistic descriptor is $S_N 2$. Reactions labeled as $S_N 2$ may be observed in several different functional group exchange reactions and the substrate and the reagent can be either simple or complex. All $S_N 2$ reactions can be represented by the simple reaction sequence: $68 \rightarrow 70$, which proceeds by a pentacoordinate transition state (69).^{154b} This scheme arises from many experimental observations in a wide variety of $S_N 2$ type reactions and no intermediate has ever been detected. The primary features of the reaction have been determined by many years of experiments and include (1) it follows second order kinetics, (2) inversion of configuration at the stereogenic center in chiral molecules and (3) the dependence of the reaction rate on the structure of the halide.



Approach of the nucleophile from the side of the molecule bearing the group X is unfavorable

^{87.} For examples see reference 3, pp 611-618 (halogenation of hydrocarbons), 667-676 (interconversion of halides), 779-784 (amines from alkyl halides), 889-910 (ethers by alkylation of alcohols), 970-972 (alcohol by halide substitution), and pp 1717-1808 (alkylation and substitution of nitriles and acid derivatives).

due to electrostatic and steric repulsion. Approach from the side opposite X (backside or anti attack) will minimize these repulsive forces and is energetically preferred. To initiate the reaction, the nucleophile collides with the δ^+ carbon, and transfers two electrons to that carbon. These two electrons are used to form a new bond, and the C-X bond is broken with both of those electrons being transferred to the more electronegative heteroatom leaving group, completing the substitution process.

The experimentally observed characteristics of many of these substitution reactions led to this mechanism, which requires a five-coordinate transition state such as **69**. The transition state structure is taken to be the logical midpoint of the reaction, where the nucleophile-carbon bond is partially formed and the C-X bond is partially broken. Transition state **69** is consistent with the following observations.

- Backside attack dictates that inversion of configuration must occur in the final product, relative to the starting material. Inversion can be detected when the starting halide possesses a stereogenic carbon bearing a leaving group, as in the conversion of 68 → 69 (R¹, R² = H, alkyl, aryl).
- 2. Since the reaction requires a collision of the nucleophile and the halide,^{154a} the rate of reaction is proportional to the concentrations of both reactants and the nature of the solvent. An S_N2 reaction is termed bimolecular because it is described by the rate expression: (Rate = k [N] [halide]). The rate of reaction is also dependent upon the strength of the nucleophile (see above).¹⁵⁴ Protic solvents slow the reaction, making aprotic solvents the preferred reaction medium.
- 3. The rate of reaction is fast with MeBr and slower with secondary halides. Tertiary halides such as *tert*-butyl bromide, Me₃C–Br, do not undergo substitution via this mechanism at any reasonable rate.

The structure of the halide is critically important for a $S_N 2$ reaction, as shown in Table 2.8.⁸⁸ This table gives the rate for reaction for the reaction of alkyl bromides with potassium iodide. As the steric bulk around the carbon being attacked by iodide increases, the rate of reaction slows. This observation correlates directly with an increase in activation energy required to achieve the pentacoordinate transition state, **69**. With tertiary halides, steric hindrance in the transition state (**69**) makes the rate of an $S_N 2$ reaction so slow that for all practical purposes there is no reaction. The neopentyl system, which appears to be primary, is in fact so sterically hindered (**69**, $R^1 = H$, $R^2 = CMe_3$) that the rate of an $S_N 2$ reaction is slower than that of a tertiary halide. Methyl halides easily attain the transition state (**69**, $R^1 = R^2 = H$) and an $S_N 2$ reaction is very facile. In allyl and benzyl halides, the π -bond participates in removal of the leaving group in the transition state, and both halides react faster than bromomethane.⁸⁸

 ⁽a) Streitwieser, Jr., A. Chem. Rev. 1956, 56, 571, (b) Streitwieser, Jr., A. Solvolytic Displacement Reactions, McGraw-Hill, New York, 1962, p.13, (c) Reference 155, p.343.

R–Br + K–I —	→ R–I + K–Br	
$\begin{array}{c} \textbf{R-X} \\ MeBr \\ EtBr \\ Me_2CHBr \\ Me_3CBr \\ Me_3CCH_2Br \\ CH_2=CHCH_2Br \\ PhCH_2Br \end{array}$	Relative Rate 1 2.2x10 ⁻² 8.3x10 ⁻⁴ 5.5x10 ⁻⁵ 3.3x10 ⁻⁷ 2.3 4.0	
[Reprinted with permission from Streitwieser, Jr., A. <i>Chem. Rev.</i> 1956 , 56, 571.Copyright © 1956 American Chemical Society.]		

Table 2.8. Reaction Rates of Alkyl Halides with Potassium Iodide

MOLECULAR MODELING: Electrostatic Potential Maps and the Strengths of Nucleophiles

In addition to steric requirements, the effectiveness of a molecule to act as a nucleophile should depend on the extent to which negative charge is localized. Specifically, a molecule in which the charge is delocalized would be expected to be a poorer nucleophile than one where the charge is concentrated on a single atom. One way to rank related molecules is to compare electrostatic potential maps. The electrostatic potential is the energy felt by a positive charge as a function of location in a molecule. The more negative the electrostatic potential, the better able a molecule is to be an effective nucleophile. An electrostatic potential map colors the electron density surface for the molecule, which conveys its overall size and shape, with the value of the potential. By convention, regions on the surface that are colored red indicate areas of high negative potential (attraction of the positive charge) while regions that are colored blue indicate areas of positive potential (repulsion of the positive charge).

One after another, build the hydroxy, methoxy, *tert*-butoxy, trifluoromethoxy, trichloromethoxy and phenoxy anions and obtain their structures and electrostatic potential maps. For each anion following the first, *click* on > to the right of the (rightmost) tab at the top of the screen and select **Continue**. This will bring up a fresh builder palette while keeping this text on screen. Display the maps for all five anions simultaneously on screen. To do this, *check* the box to the left of each of the five tabs at the top of the screen. Manipulate each image in turn to best see the oxygen. It is perhaps easier to do this with transparent surfaces. *Click* on an image and select **Transparent** from the **Style** menu at the bottom of the screen. When you are done, return to solid surfaces.

Because these are negative ions, the test charge is never repelled and the maps contain no "blue regions". Focus your attention on the most "red" region (associated with the oxygen) and rank the anions in order of decreasing negative charge. You can measure the potential for a region of a map by clicking on the region. The value will be presented at the bottom of the screen. Which anion should be the "best" nucleophile? Which should be the poorest? Justify your observations.

Optional: Examine other "oxygen" nucleophiles to see if you can identify one that should be stronger than the best of those above.

MOLECULAR MODELING: Local Ionization Potential Maps and the Strengths of Nucleophiles

The previous problem examined the ability of electrostatic potential maps to account for the relative strengths of oxyanions as nucleophiles. The hypothesis was that the more negative the potential at oxygen, the more nucleophilic the anion. An alternative but closely-related measure of nucleophile strength is provided by local ionization potential maps. What is depicted here is not the energy between a positive test charge and the nuclei and electrons of a molecule as a function of location, but rather the energy required to eject ("ionize") an electron from a particular location on the surface. Neither the energy required to eject an electron from a molecule can be measured (it is the ionization potential).

Examine local ionization potential maps for hydroxy, methoxy, *tert*-butoxy, trifluoromethoxy, trichloromethoxy and phenoxy anions (left to right, top to bottom on screen). (*SpartanModel* cannot calculate local ionization potential maps and these results were obtained from *Spartan*.) By convention, regions on the surface that are colored red indicate areas where while regions that are colored blue indicate regions where ionization is difficult. You are looking to compare regions of low ionization potential ("red" regions). The maps are initially displayed as transparent models to allow you to see the underlying structures. Once you are oriented, switch to solid models to facilitate comparison of the maps. *Click* on one of the maps and select *Solid* from the **Style** menu at the bottom of the screen.

Which anion should be the "best" nucleophile? Which should be the poorest? It might help you to measure the value of the local potential for the appropriate region of a map. *Click* on this region and the value will be presented at the bottom of the screen. Is the ordering of nucleophile strengths the same as that found from electrostatic potential maps?

MOLECULAR MODELING: Solvent Effects on S_N2 Reactions

Quantum chemical calculations refer strictly to isolated molecules, that is, molecules in the gas phase. While it is not yet practical to carry out calculations with explicit solvent, it is possible to empirically correct the gas-phase calculations to account (at least qualitatively) for the effects of solvent. Caution is required as the solvation models are primitive, taking into account only "bulk" effects and ignoring individual interactions, most important, individual hydrogen bonds.

Consider, for example, the role of the solvent on the equilibrium between chloride ion and methyl iodide on one side and methyl chloride and iodide ion on the other. In solution, the reaction as written is known to be *exothermic*, that is, chloride displaces iodide. Iodide is said to be the better *leaving group*.

$$CI^{-} + \underbrace{H_{H'}}_{H} C^{-} I \xrightarrow{H} CI^{-} CI^{-} C_{H'} H^{+} I^{-}$$

Examine energy profiles for $S_N 2$ reaction of chloride and methyl iodide obtained from quantum chemical calculations. This starts from "separated" chloride anion and methyl iodide, proceeds through the transition state involving five coordinate carbon, and goes onto methyl chloride and iodide anion. The black curve corresponds to the reaction in the gas, and the red curve corresponds
MOLECULAR MODELING: Solvent Effects on S_N2 Reactions, con't.

to reaction in "water", that is, data on the isolated molecule have been empirically corrected to account for the effects of the solvent. Do the solvent-corrected calculations reproduce the known direction of the equilibrium, that is, is the reaction *exothermic* in solvent? Is the reaction *endothermic*, *exothermic* or thermoneutral in the gas phase?

The electrostatic potential map for one step in the overall reaction sequence is shown on screen. This indicates what a point positive charge "feels" at different regions on the accessible surface of molecule. If the charge is attracted this suggests that the region on the surface is locally "negative". If it is repelled, this suggests that the region is locally positive. By convention, "negatively-charged" regions on the surface are colored "red", "positively-charged" regions are colored "blue" and neutral regions are colored "green". Because this is a negative ion, there are no blue regions. The map is shown as a transparent model, which means that you can also see the underlying structure (Cl on the left and I on the right). You can switch to a solid model by *clicking* on the map and selecting *Solid* from the **Style** menu at the bottom of the screen. This will allow you to better assess the transfer of charge as the reaction proceeds.

To "visualize" the transfer of negative charge from chloride to iodide, step through the sequence of electrostatic potential maps using the **Step** keys at the bottom left of the screen, or "animate" the sequence using the **Play** key. Note that this data refers to the gas phase as the solvent corrections discussed above apply only to energies. For which side of the reaction is the negative charge more extreme? Given this result, are the reactants or products likely to be more stabilized by the solvent? Elaborate. Is this consistent with any change in energy between isolated molecule and solvated calculations that you previously observed?

The $S_N 2$ reaction is a powerful method for incorporating functional groups into a carbon skeleton, but the mechanism of the reaction imposes several important synthetic restrictions. The poor reactivity of sterically hindered halides dictates that primary or secondary substrates be used, and inversion of configuration makes the reaction suitable for manipulating stereochemistry. A typical example is the $S_N 2$ reaction of cyanide ion with the primary tosylate, formed by reaction of alcohol **71** with tosyl chloride, to give nitrile **72** in 80% overall yield, taken from Panek and Zhang's synthesis of herboxidiene/GEX 1A.⁸⁹



An S_N^2 reaction using the nucleophilic azide anion is another good way to introduce nitrogen into a molecule, with control of stereochemistry and usually without the complications often accompanying the use of amine nucleophiles (elimination, salt formation, reversibility). An example is the conversion of one hydroxyl unit in diethyl *L*-tartrate **73** to azide **74** in 74% yield,

^{89.} Zhang, Y.; Panek, J.S. Org. Lett. 2007, 9, 3141.

with clean inversion of configuration, in Overman and co-worker's synthesis of (–)-sarain A.⁹⁰ Note that the polar aprotic solvent DMSO was used to maximize the yield of S_N2 products and suppress side reactions such as elimination (secs. 2.7, 2.9.A). Alkyl azides can be explosive, however, so care should be exercised when azide in used. Typical S_N2 reactions involve functional group transforms such as $Br \rightarrow OMe$, $OTs \rightarrow N_3 \rightarrow NH_2$ and $Cl \rightarrow I$, showing the range and power of this reaction in synthesis. Many other types of nucleophilic reactions are possible, including reactions of enolate anions with alkyl halides (sec. 9.3.A), which proceed via an $S_N 2$ pathway.⁹¹ A classical reaction that involves a $S_N 2$ reaction is the Williamson ether synthesis, ⁹² illustrated by the conversion of the OH unit in 75 to the alkoxide, allowing $S_N 2$ displacement of one bromide in 1,2-dibromodecane to give ether 76 in 65% yield in Thelakkat and co-worker's synthesis of a donor acceptor dyad (donor-bridge acceptor), used for the study of energy- and electron transfer processes in organic semiconductors.⁹³ Intramolecular Williamson ether syntheses are possible. In a synthesis of galanthamine, Tu and co-workers showed that treatment of 77 with the base DBU converted the -O-SiMe₂t-Bu group to the alkoxide (RO⁻), which displaced the bromide to form the benzofuran unit in 78, in 90% yield.⁹⁴ The use of microwaves in conjunction with phase transfer catalysis is also quite effective in these reactions.95



Becker, M.H.; Chua, P.; Downham, R.; Douglas, C.J.; Garg, N.K.; Hiebert, S.; Jaroch, S.; Matsuoka, R.T.; Middleton, J.A.; Ng, F.W.; Overman, L E. J. Am. Chem. Soc. 2007, 129, 11987..

- 91. For a synthetic example, see Marshall, J.A.; Ellison, R.H. J. Am. Chem. Soc. 1976, 98, 4312.
- 92. (a) Williamson, A.W. J. Chem. Soc. 1851, 4, 229; (b) Dermer, O.C. Chem. Rev. 1934, 14, 385 (see p 409); (c) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-101.
- 93. Bauer, P.; Wietasch, H.; Lindner, S.; Thelakkat, M. Chem. Mater. 2007, 19, 88.
- 94. Hu, X.-D.; Tu, Y. Q.; Zhang, E.; Gao, S.; Wang, S.; Wang, A.; Fan, C.-A.; Wang, M. Org. Lett. 2006, 8, 1823.
- 95. For a review of microwave activation in phase transfer catalysis see Deshayes, S.; Liagre, M.; Loupy, A.; Luche, J.-L.; Petit, A. *Tetrahedron* 1999, 55, 10851.

The reactions involving **71**, **73**, and **75** used three different types of nucleophiles, cyanide, an azide, and an alkoxide. The ability to evaluate the relative strength and effectiveness of different nucleophiles is obviously as important for $S_N 2$ reactions as it was for nucleophilic acyl substitution reactions. A general list of nucleophiles in order of their ability to form bonds to sp³ carbon in a $S_N 2$ reaction is:

where the dominant factor is assumed to be polarizability.¹⁰¹

Nucleophilic strength depends on two factors, the nature of the substrate (*s*) and the strength of the nucleophile, measured by its nucleophilicity (*n*). Nucleophilic strength for a given species is given by the **Swain-Scott equation**^{96a} [log (k/k_0) = (*s*) (*n*)], where *n* = 0 for water at 25°C, *s* = 2.00 for bromomethane,^{97a} and *n* is a reagent parameter measuring nucleophilic power in a particular system. The parameter *s* is the susceptibility of the substrate (here an halide) to being attacked (it measures the power of a substrate to discriminate between various nucleophiles). An electrophilicity index has been established based on electronegativity divided by chemical hardness.^{96b,c} The important qualitative message of this equation is that nucleophilic strength varies with the substrate. Table 2.9 gives a partial list of nucleophiles,⁹⁷ ordered by use of the Swain-Scott equation⁹⁶ for their reaction with bromomethane. This list constitutes a general order of nucleophilic strength in S_N2 reactions. It is known that the nucleophilicity order differs for S_N2 reactions when compared with acyl addition to a carbonyl (secs. 2.6.A,B and 2.5), and tends to follow more closely the order established for basicity [the carbonyl carbon is a harder acid than saturated carbon (sec. 2.4.C)].

There are obviously several parameters contributing to nucleophilic strength, and a few general statements can be made. *1*. A nucleophile with a negative charge is stronger than its conjugate acid. $NH_2^- > NH_3$ and $HO^- > HOH$. *2*. In the same row, nucleophilicity parallels basicity, and $R_3C^- > R_2N^- > RO^- > F^-$.

Rules 1 and 2 predict the following order for nucleophilic strength:

 $\label{eq:horizon} \begin{array}{l} NH_2^- > RO^- > HO^- > R_2NH > ArO^{-*} > NH_3 > C_5H_5N > F^- > HOH > ClO_4^{-**} \\ {}^* \text{less nucleophilic due to resonance delocalization} \\ {}^{**} \text{ charge spread out due to resonance, less nucleophilic} \end{array}$

^{96. (}a) Swain, C.G.; Scott, C.B. J. Am. Chem. Soc. 1953, 75, 141; (b) Parr, R.G.; Szentpály, L.V.; Liu, S. J. Am. Chem. Soc. 1999, 121, 1922; (c) Maynard, A.T.; Huang, M.; Rice, W.G.; Covel, D.G. Proc. Natl. Acad. Sci. USA 1998, 95, 11578.

^{97.} Edwards, J.O.; Pearson, R.G. J. Am. Chem. Soc. 1961, 84, 16.

Table 2.9. Nucleophilic Strength with Bromoethane as Ordered by the Swain-ScottEquation

Nucleophile	n	Nucleophile	n	Nucleophile	n
$S_2O_3^{2-}$	6.35	SO3 ²⁻	5.67	⁻ CN	5.13
PO_4^-	5.06	I	4.93	⁻ SCN	4.80
CO_{3}^{2-}	4.36	HO ⁻	4.23	¯OPh	4.16
Br ⁻	4.02	N_3^-	3.92	⁻OPhp–Cl	3.86
NO_2^-	3.71	HPO ₃ ⁻	3.52	$B_2 O_7^{2-}$	3.45
p-NO ₂ PhO ⁻	3.08	Cl-	2.99	AcO ⁻	2.76
HCO_2^-	2.62	HSO ₃ ⁻	2.3	$H_2PO_4^-$	2.2
F ⁻	1.88	SO_4^{2-}	2.1	HNO ₃ ⁻	2.1
HSO_4^-	2.1	ClO_3^-	2.1	ClO_4^-	2.1
НОН	0.01				
[Reprinted with permission from Edwards, J.O.; Pearson, R.G. J. Am. Chem. Soc. 1961, 84, 16. Copyright ©1961 American Chemical Society.]					

Nucleophilic strength for a given substituent can be measured in terms of the rate of the $S_N 2$ reaction or the rate in reactions with carbonyl derivatives.⁹⁸ The relative rates of several nucleophiles determined by reaction with iodomethane are shown in Table 2.10.⁹⁹ Electronic effects are important as illustrated by methoxide, where the electron releasing methyl group makes methoxide more nucleophilic relative to hydroxide. The rate of the $S_N 2$ reaction of sodium hydroxide with iodomethane is $1.3 \times 10^{-4} M^{-1} s^{-1}$ whereas the rate with sodium methoxide with iodomethane is $2.51 \times 10^2 M^{-1} s^{-1}$.⁹⁹

 Table 2.10. Relative Rates of Reaction of Nucleophiles with Iodomethane

Nucleophile	$k (\text{x10}^{-3} \text{ M}^{-1} \text{ s}^{-1})$
MeO	0.251
\mathbf{F}^{-}	0.00005
NHEt ₂	2.2
PhO ⁻	0.073
NH ₃	0.041
pyridine	0.022

A species is less nucleophilic if there is resonance delocalization of the electron density. An example is the phenoxide anion, where the electrons on oxygen are delocalized away from oxygen by the adjacent phenyl ring, meaning that oxygen cannot donate electrons as effectively. Phenoxide is less nucleophilic than an alkoxide that is incapable of resonance, such as methoxide. Nucleophilic reactions are usually under kinetic control whereas acidbase reactions are under thermodynamic control. Under kinetic control, the most nucleophilic

^{98. (}a) Hudson, R.F.; Green, M. J. Chem. Soc. 1962, 1055, (b) Bender, M.L.; Glasson, W.A. J. Am. Chem. Soc. 1959, 81, 1590, (c) Jencks, W.P.; Gilchrist, M. Ibid 1965, 90, 2622.

^{99.} Pearson, R.G.; Sobel, H.; Songstad, J. J. Am. Chem. Soc. 1968, 90, 319.

species will react faster in substitution reactions.

3. Going down the periodic table, nucleophilicity increases but basicity decreases $[I^- > Br^- > Cl^- > F^-$ (this ordering is solvent dependent), and $(RS^- > RO^-)]$.

Comparing the rate of reaction of MeI with PhSe⁻ [7000 x 10³ M⁻¹s⁻¹], PhS⁻, [1070 x 10³ M⁻¹s⁻¹] and PhO⁻ [0.073 x 10³ M⁻¹s⁻¹] shows the trend mentioned in (*3*).⁹⁹ Likewise, trialkylphosphines are more nucleophilic than trialkylamines ($R_3P > R_3N$). The rate of reaction of Et₃P with iodomethane is 1.29 x 10³ M⁻¹s⁻¹ whereas the rate for Et₃N is 0.595 x 10³ M⁻¹s⁻¹.⁹⁹ These latter reactions are particularly useful in organic synthesis. Phenoxide is commonly used in S_N2 reactions for the preparation of phenyl (or aryl) ethers, a structural unit found in many naturally occurring molecules. Thiophenol is used to generate phenyl sulfides via the thiophenoxide anion, and phenyl selenides can be formed from the phenyl selenide anion. Oxidation of the sulfide or selenide generates the corresponding sulfoxide (*S*-O) or selenoxide (*Se*-O), which are subject to thermal syn elimination to form the corresponding alkene¹⁰⁰ (secs. 2.9.C.v, 2.9.C.vi). These transformations are used to introduce an alkenyl unit into the molecule. Thioalkyl groups are also used to enhance the acidity of the adjacent hydrogen and the chemistry of sulfurstabilized carbanions is important for reactions that generate carbon–carbon bonds, including many of the Umpolung reagents (sec. 8.6.B).

The reaction of trialkylphosphines, especially triphenylphosphine, with alkyl halides is particularly useful since the resultant phosphonium salts are easily converted to a phosphonium ylid on treatment with a suitable base (sec. 8.8.A). Ylids are, of course, the reactive species in the well-known **Wittig olefination** reaction,¹⁰¹ which will be discussed in section 8.8.A.i. A related $S_N 2$ process involves reaction of a trialkylphosphite with an alkyl halide, the **Arbuzov reaction** (sometimes called the **Michaelis-Arbuzov reaction**).¹⁰² Triethylphosphite (**79**) reacts with iodomethane to give the phosphonium salt, **80**. Heating generates the monoalkyl phosphonic ester (**81**). This type of phosphonic ester can be converted to an ylid and used in the well-known **Horner-Wadsworth-Emmons olefination**¹⁰³ (sec. 8.8.A.iii).



^{100.} DePuy, C.H.; King, R.W. Chem. Rev. 1960, 60, 431.

⁽a) Wittig, G.; Schöllkopf, U. Berichte 1954, 87, 1318; (b) Wittig, G.; Haag, W. Berichte 1955, 88, 1654;
(c) Trippett, S. Quart. Rev. Chem. Soc. (London) 1963, 17, 406; (d) Wittig, G. Acc. Chem. Res. 1974, 7, 6.

^{102. (}a) Michaelis, A.; Kaehne, R. Berichte 1898, 31, 1048; (b) Arbuzow, A.E. J. Russ. Phys. Chem. Soc. 1906, 38, 687; (c) Idem Chem. Zentr., 1906, II, 1639; (d) Arbuzow, B.A. Pure Appl. Chem. 1964, 9, 307; (e) Kosolapoff, G.M. Org. React. 1951, 6, 273 (see pp 276-277).

^{103. (}a) Wadsworth, W.S.; Emmons, W.D. J. Am. Chem. Soc. 1961, 83, 1733; (b) Boutagy, R.; Thomas, Jr., R. Chem. Rev. 1974, 74, 87.

The analogous but slower reaction with amines can be used to form ammonium salts. When the ammonium salt has a hydrogen atom on the carbon β - to the nitrogen atom, these salts are useful in the **Hoffmann elimination** sequence (sec. 2.9.C.i).¹⁰⁴ Triphenylamine reacts with iodomethane to give methyltriphenylammonium iodide (MePh₃N⁺I⁻) and alkyl ammonium salts such as this can be used as phase-transfer catalysts.¹⁰⁵ Phase transfer ammonium salts often contain large alkyl groups (dodecyl, hexadecyl, and octadecyl), and sometimes small groups. Tetrabutylammonium chloride is a useful phase-transfer reagent.

Substitution by amines or phosphines with an alkyl halide is clearly an $S_N 2$ type process. Normally, the presence of water in the reaction medium suppresses the rate of $S_N 2$ reactions because they usually involve the reaction of a charged nucleophile and a neutral substrate. An exception can occur, however, if both starting materials are neutral but the products are charged, as in the reaction of amines with alkyl halides. This reaction generates transition state 82 with a δ + nitrogen and a δ - halogen. A protic solvent will separate the developing charge in this transition state, ultimately leading to the solvent separated ions $^+NRH_2R'$ and X^- . Solvation and ion separation therefore accelerates the S_N2 process in this preparation of ammonium salts. Amine alkylation of this type finds its way into synthesis. An interesting example is taken from Loh and Lee's synthesis of (-)-epibatidine,¹⁰⁶ in which the intramolecular displacement of one bromide in 83 gave an 85% yield of 84. Polyalkylation is sometimes a problem when amines or ammonia react with alkyl halides, and amine surrogates are often used, including phthalimide. In a synthesis of a mitochondrial complex 1 inhibitor,¹⁰⁷ Radeke and co-workers prepared phthalimide 86 from benzylic bromide 85, by initial coupling with phthalimide in 86% yield followed by three steps to convert the aryl iodide to the hydroxy-butyl unit. Final treatment with hydrazine in refluxing butanol liberated the amino group in 87 in 84% yield, with phthalhydrazide (88) as a by-product.

$$RNH_{2} + \underset{R^{3}}{\overset{R^{1}}{\underset{R^{3}}{\longrightarrow}}} X \longrightarrow \begin{bmatrix} H_{\delta^{+}} & R^{1} \\ R-N-\frac{1}{2} & -\frac{\delta^{-}}{2} \\ H & R^{2}R^{3} \end{bmatrix} \longrightarrow \begin{array}{c} H_{\delta^{+}} & R^{1} \\ R-N-\frac{1}{2} & -\frac{\delta^{-}}{2} \\ H & R^{2}R^{3} \end{bmatrix} \xrightarrow{} \begin{array}{c} H_{\delta^{+}} & R^{1} \\ R-N-\frac{1}{2} & -\frac{\delta^{-}}{2} \\ H & R^{3} \end{bmatrix} \xrightarrow{} \begin{array}{c} H_{\delta^{+}} & R^{1} \\ R-N-\frac{1}{2} & -\frac{\delta^{-}}{2} \\ H & R^{3} \end{bmatrix} \xrightarrow{} \begin{array}{c} H_{\delta^{+}} & R^{1} \\ R-N-\frac{1}{2} & -\frac{\delta^{-}}{2} \\ H & R^{3} \end{bmatrix} \xrightarrow{} \begin{array}{c} H_{\delta^{+}} & R^{1} \\ R-N-\frac{1}{2} & -\frac{\delta^{-}}{2} \\ H & R^{3} \end{array}$$

^{104. (}a) Hofmann, A.W. Annalen 1851, 78, 253; (b) Hofmann, A.W. Annalen 1851, 79, 11; (c) Brown, H.C.; Moritani, I. J. Am. Chem. Soc. 1956, 78, 2203; (d) Cope, A.C.; Trumbull, E.R. Org. Reactions, 1960, 11, 317; (e) Hofmann, A.W. Berichte 1881, 14, 659; (f) Wall, E.N.; McKenna, J. J. Chem. Soc. B, 1970, 318; (g) Wall, E.N.; McKenna, J. J. Chem. Soc. C 1970, 188; (h) Bach, R.D.; Bair, K.W.; Andrezejewski, D. J. Am. Chem. Soc. 1972, 94, 8608; (i) Archer, D.A.; Booth, H. J. Chem. Soc. 1963, 322.

 ^{105. (}a) Jones, R.A. Aldrichimica Acta 1976, 9, 35; (b) Starks, C.M. J. Am. Chem. Soc. 1971, 93, 195; (c) Starks, C.M.; Owens, R.M. J. Am. Chem. Soc. 1973, 95, 3613; (d) Herriott, A.W.; Picker, D. J. Am. Chem. Soc. 1975, 97, 2345.

^{106.} Lee, C.-L.K., Loh, T.-P. Org. Lett. 2005, 7, 2965.

^{107.} Radeke, H.; Hanson, K.; Yalamanchili, P.; Hayes, M.; Zhang, Z.-Q.; Azure, M.; Yu, M.; Guaraldi, M.; Kagan, M.; Robinson, S.; Casebier, D. J. Med. Chem. 2007, 50, 4304.



4. Greater steric encumbrance diminishes nucleophilicity. Comparing reactions with pyridine and 2,6-dimethylpyridine (2,6-lutidine) illustrates this point. The rate of reaction of pyridine with methyl iodide is $0.022 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$. The two methyl groups proximal to the nitrogen atom in 2,6-lutidine sterically encumber approach of nitrogen to the carbon of methyl iodide, and the rate declines to $0.00042 \times 10^3 \text{ M}^{-1}\text{s}^{-1}$, about 50 times slower.⁹⁹ As pyridine approaches the electrophilic carbon, the ortho hydrogens interact with the alkyl groups on that carbon, but this represents a minimal steric interaction when compared to the ortho-methyl groups in 2,6lutidine.

A key feature of $S_N 2$ reactions is inversion of configuration at the electrophilic center (see $73 \rightarrow 74$ and $83 \rightarrow 84$ above). The $S_N 2$ reaction is an effective method for inversion of the stereocenter with insertion of a different functional group. Alcohols are convenient synthetic intermediates, but the OH moiety is a poor leaving group (sec. 2.7.E). Conversion of the OH unit into an ester, sulfonate ester or phosphonate derivative often allows an $S_N 2$ type displacement to proceed, with inversion of that stereogenic center.

2.6.A.ii. The Mitsunobu Reaction. If one sets a goal of inverting the stereochemistry of 2(S)-pentanol to form 2(R)-pentanol, there is a problem. Hydroxide will not displace OH, and if the OH unit is converted to a halide or sulfonate ester, treatment with hydroxide can lead to elimination as a major competitive reaction. The use of nucleophile such as acetate would minimize elimination, but acetate is a poor nucleophile for substitution reaction. There are many times when a nucleophile is too weak for facile $S_N 2$ displacement, and substitution is also difficult if the substrate contains a poor leaving group. A successful and highly useful solution to this problem is the Mitsunobu reaction.¹⁰⁸ This procedure is typically used to invert the

 ⁽a) Mitsunobu, O. Synthesis 1981, 1; (b) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-62.

stereochemistry of an alcohol by converting a poor leaving group to an excellent leaving group for subsequent reaction with a nucleophile. A synthetic example shows the conversion of (*R*)alcohol **89** to (*S*)-alcohol **90** in 51% overall yield using diethyl azodicarboxylate (DEAD, **91**), *p*-nitrobenzoic acid and triphenylphosphine, followed by saponification of the resulting ester with LiOH in aqueous methanol in a synthesis of (+)-ricciocarpin A by Liu and Jan.¹⁰⁹ As initially formulated, the process involved reaction of **91** with triphenylphosphine (Ph₃P) to form **92**. Disopropyl azodiacarboxylate (DIAD) is commonly used in this reaction rather than DEAD. Dipolar ion **92** reacts with HX, which is present in the initial reaction, to give phosphonium salt **93**. An alcohol is then added and the subsequent reaction generates alkoxyphosphonium salt **95** and diimide **94**. Displacement of triphenylphosphine oxide (a neutral leaving group) by X



gives the substitution product, R-X. The X moiety in HX can be a variety of groups, including carboxylate, azide, imido, and R (an active methylene compound such as malonate or an α -cyanoester).¹⁰⁸ As suggested by the range of functional groups cited, there are many variations. In one, taken from DeBrabender and co-worker's synthesis of gustastatin,¹¹⁰ selective etherification of one phenolic OH unit in **96** gave benzyl ether **97** in 73% yield. Note the use of DIAD in this reaction. Lepore and He have shown that ether formation via the Mitsunobu reaction is facilitated with sonication.¹¹¹ Ghosh and Moon reported an example of what may be the most common application of the Mitsunobu reaction in an enantioselective synthesis of (+)-jasplakinolide,¹¹² where the alcohol unit in **98** was converted to the *p*-nitrobenzoate ester with clean inversion of configuration, and then hydrolyzed to the alcohol in **99** in 78% yield. Recent work to improve this reaction has focused on several aspects of the reaction,¹¹³ including the use of alternative reagents, phase-switching modifications of phosphine, azodicarboxylate,

^{109.} Jan, N.-W.; Liu, H.-J. Org. Lett 2006, 8, 151.

^{110.} Garcia-Fortanet, J.; Debergh, J.R.; De Brabander, J.K. Org. Lett. 2005, 7, 685.

^{111.} Lepore, S.D.; He, Y. J. Org. Chem. 2003, 68, 8261.

^{112.} Ghosh, A.K.; Moon, D.K. Org. Lett. 2007, 9, 2425.

^{113.} Dembinski, R. Eur. J. Org. Chem. 2004, 2763.

and nucleophilic components are emphasized and also the separation of products from byproducts¹¹⁴ using fluorous compounds.



Other transformations are possible. The reaction of succinimide with 2-propanol under Mitsunobu conditions gave N-isopropyl succinimide in 73% yield.¹¹⁵ Hydroxyl can also be replaced with other functional groups using this method. Mitsunobu coupling can be used to insert functional groups that might be difficult to prepare under other conditions. As just discussed, reaction of an alcohol and an acid,¹¹⁶ generates an ester. Azides can be conveniently prepared, as illustrated in Banwell and co-worker's synthesis of (+)-brunsvigine,¹¹⁷ in which (S)alcohol 100 was converted to (R)-azide 101 in 93% yield using Mitsunobu conditions. Note that the reagent diphenylphosphoryl azide (DPPA) was used, since it is often more efficient than the KN₃ or NaN₃ reagents.¹¹⁸ Alcohols react with phthalimide under Mitsunobu conditions to give the N-substituted phthalimide, which can be unmasked to the primary amine by reaction with hydrazine, as noted above.¹¹⁹ This latter reaction of phthalimide with alkyl halides followed by treatment with hydrazine is a variation of a classical reaction called the Gabriel synthesis.¹²⁰ The use of hydrazine in this manner is called the **Ing-Manske modification**¹²¹ of the Gabriel synthesis. The use of Mitsunobu conditions simply expands the reaction to include alcohols as starting materials. The same transformation has been accomplished using TsNHCO₂t-Bu (abbreviated TsNHBoc) to incorporate a nitrogen moiety.¹²²

^{114.} Dandapani, S.; Curran, D.P. Chem. Eur. J. 2004, 10, 3131.

^{115.} Reference 108, p 5.

^{116.} For an example, see Keck, G.E.; McHardy, S.F.; Murry, J.A. J. Org. Chem. 1999, 64, 4465.

^{117.} Banwell, M.G.; Kokas, O.J.; Willis, A.C. Org. Lett. 2007, 9, 3503.

^{118.} See Lal, B.; Pramanik, B.N.; Manhas, M.S.; Bose, A.K. Tetrahedron Lett. 1977, 18, 1977.

For examples, see (a) Brosius, A.D.; Overman, L.E.; Schwink, L. J. Am. Chem. Soc. 1999, 121, 700; (b) Mulzer, J.; Scharp, M. Synthesis 1993, 615.

⁽a) Gabriel, S. Berichte 1887, 20, 2224; (b) Gibson, M.S.; Bradshaw, R.W. Angew. Chem. Int. Ed. 1968, 7, 919; (c) Mundy, B.P.; Ellerd, M.G.; Fabaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis 2nd Ed. Wiley, New York, 2005, pp 264; (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-36.

^{121.} Ing, H.R.; Manske, R.H.F. J. Chem. Soc. 1926, 2348.

^{122.} Trost, B.M.; Oslob, J.D. J. Am. Chem. Soc. 1999, 121, 3057.



Another modification of the Mitsunobu reaction illustrates two features that can be useful in synthesis. When **102** was treated with triphenylphosphine and DEAD, cyclization occurred to give benzoxepin **103** in 87% yield.¹²³ This example shows that Mitsunobu conditions can be used for intramolecular reactions, and also that an alcohol can be coupled with another OH unit. Yamaguchi and co-workers used this transformation in a synthesis of radulanins.¹²³



The Mitsunobu reaction is a clever and highly useful exploitation of the S_N2 reaction that allows one to control the stereochemistry of a given stereogenic center (see Chap. 6). It also allows one to correct the stereochemistry if an alcohol is produced that has the opposite stereochemistry from that desired (sec. 6.2.B).

2.6.A.iii. The $S_N 2$ ' Reaction. Normal $S_N 2$ reactions were illustrated in the previous sections. In general, allylic halides react faster with nucleophiles than do simple alkyl halides (see above) because the π bond can participate in expulsion of the leaving group. If the leaving group bearing

$$S_{N^{2}} \xrightarrow{R} \xrightarrow{C \equiv N} \xrightarrow{R} \xrightarrow{X} \qquad S_{N^{2'}} \xrightarrow{R} \xrightarrow{C \equiv N} \xrightarrow{R} \xrightarrow{X}$$

carbon becomes too sterically hindered in the allylic system, however, the normal $S_N 2$ path is inhibited and an alternative mode of attack occurs, at the end of the π system. Such attack is termed an $S_N 2$ ' reaction¹²⁴ (nucleophilic bimolecular substitution with allylic rearrangement). The retrosynthetic analysis of each reaction, using cyanide as the nucleophile, offers a useful comparison, especially for regiochemical differences in the product distribution. The two pathways often compete and can lead to annoying mixtures of regioisomers, although the reaction may be synthetically useful. Formation of piperidine derivative **105** via the $S_N 2'$ displacement of the allylic 3,5-dichlorobenzoate (**104**) is an excellent example of this process.¹²⁵

^{123.} Yamaguchi, S.; Furihata, K.; Miyazawa, M.; Yokoyama, H.; Hirai, Y. Tetrahedron Lett. 2000, 41, 4787.

^{124.} Magid, R.M. Tetrahedron 1980, 36, 1901.

 ^{125. (}a) Stork, G.; White, W.N. J. Am. Chem. Soc. 1953, 75, 4119; (b) Stork, G.; White, W.N. Ibid 1956, 78, 4609; (c) Stork, G.; Kreft III, A.F. Ibid 1977, 99, 3850, 8373.

The nucleophile attacks the π bond since the *O*-benzyl carbon is sterically encumbered. The π bond assists the removal of the leaving group in an S_N2' reaction.



The S_N2' reaction proceeds with a high degree of stereochemical control, as in the nucleophilic displacement $104 \rightarrow 105$. Bordwell and co-workers described the S_N2' reaction with amines as second order, but invoked a tight ion pair to explain the process.¹²⁶ A tight ion pair will have significant ionic character, but the ions are not solvent separated. Smith and coworker's work with cyclopropylcarbinyl halides supports this mechanistic rationale. Reaction of piperidine with the *tert*-butyl derivative $(106)^{127}$ gave the expected 107 in 88% yield but also 8% of 109. Formation of this latter product is not compatible with a simple S_N2 displacement due to the great steric hindrance imposed by the neopentyl-like structure, but the tight ion pair mechanism explains the presence of 108 very well. When it can be applied as the major process, stereochemical and regiochemical control makes the S_N2' reaction a useful tool in synthetic planning. With other allylic substrates, the possibility of this reaction as a competitive side reaction must be acknowledged as a process that can diminish the yield of the S_N2 product.



A synthetic example of an $S_N 2$ ' reaction is the conversion of **109** to a tertiary bromide with phosphorus tribromide. Subsequent reaction with the sodium salt of thiophenol gave an $S_N 2$ '

^{126. (}a) Bordwell, F.G.; Pagani, G.A. J. Am. Chem. Soc. 1975, 97, 118; (b) Bordwell, F.G.; Mecca, T.G. Ibid 1975, 97, 123, 127; (c) Bordwell, F.G.; Wiley, P.F.; Mecca, T.G. Ibid 1975, 97, 132.

^{127. (}a) Smith, M.B.; Hrubiec, R.T.; Zezza, C.A. J. Org. Chem. 1985, 50, 4815; (b) Hrubiec, R.T.; Smith, M.B. Tetrahedron Lett. 1983, 24, 5031.

displacement to give 110 in Itô and co-worker's synthesis of neocembrene.¹²⁸

Organocuprates (sec. 8.7.A) react via an $S_N 2$ ' type process in some cases.¹²⁹ The organocuprate reaction may actually proceed by copper stabilized radical intermediates, rather than a formal $S_N 2$ ' mechanism.¹³⁰ Magnesium cuprates also undergo $S_N 2$ ' reactions, as in the conversion of tertiary allylic acetate **111** to **112**, in 72% yield.¹³¹ Note that the displacement proceeded with good diastereoselectivity for the anti-diastereomer **112**. An $S_N 2$ ' like reaction has also been observed in reactions of organocuprates with cyclopropylcarbinyl halides, where the strained cyclopropane ring behaves similarly to the π bond of an alkene.¹³²



2.6.A.iv. $S_N 2$ Type Reactions with Epoxides. Epoxides are highly reactive, and many nucleophiles can open the three-membered ring to give a substituted or functionalized alcohol. Nucleophilic opening on an epoxide in aprotic solvents is best described as an $S_N 2$ reaction. The nucleophile attacks the less sterically hindered carbon atom in 113 to give alkoxide 114, and subsequent protonation gives alcohol 115. In Feldman and Saunders' synthesis¹³³ of (–)-agelastatin A, epoxide 116 was treated with sodium azide, and the resulting alkoxide was protonated with aqueous ammonium chloride to give azido alcohol 117.



In another example, the nucleophile attacked the more substituted site. In Baskaran and coworker's synthesis of indolizidine 167B,¹³⁴ initial reaction of the epoxide unit in **118** with a

- 133. Feldman, K.S.; Saunders, J.C. J. Am. Chem. Soc. 2002, 124, 9060.
- 134. Reddy, P.G.; Varghese, B.; Baskaran, S. Org. Lett. 2003, 5, 583.

^{128.} Kodama, M.; Matsuki, Y.; Itô, S. Tetrahedron Lett. 1975, 3065.

^{129.} For older examples, see (a) Kreft, A. Tetrahedron Lett. 1977, 1035; (b) Trost, B.M.; Tanigawa, Y. J. Am. Chem. Soc. 1979, 101, 4413.

 ⁽a) Johnson, C.R.; Dutra, G.A. J. Am. Chem. Soc. 1973, 95, 7777, 7783; (b) Ashby, E.C.; DePriest, R.N.; Tuncay, A.; Srivastava, S. Tetrahedron Lett. 1982, 23, 5251.

^{131.} Belelie, J.L.; Chong, J.M. J. Org. Chem. 2002, 67, 3000.

 ^{132. (}a) Hrubiec, R.T.; Smith, M.B. *Tetrahedron* 1984, 40, 1457; (b) *Idem J. Org. Chem.* 1984, 49, 385; (c) Posner, G.H.; Ting, J.-S.; Lentz, C.M. *Tetrahedron* 1976, 32, 2281.

Lewis acid (BF_3) generated an oxonium ion, and reduction of the azide gave a primary amine, and attack of the ion paired system at the more hindered site gave **119** in 50% overall yield.



2.6.B. UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION

Unimolecular substitution (ionization followed by substitution, $S_N 1$) is generally less useful in synthesis, but may be the best specific reaction to give a particular functional group exchange. In Chapter 12 we will see many examples where cationic reactions are useful. Unimolecular substitution occurs as a side reaction in aqueous media, and the extent of ionization can influence the yield, stereochemistry and regiochemistry of the final product.

2.6.B.i. Carbocations (Carbenium ions). A carbocation is an electron-deficient reaction intermediate bearing an sp² hybridized carbon that is, in effect, an empty p orbital. Such species are now called carbenium ions, but since we are focusing on the ionic nature of intermediates the older term will be used throughout. Carbocations are key electrophilic intermediates in many ionization reactions, as will be discussed in Chapter 12, and react with many suitable nucleophiles. From a mechanistic standpoint, ionization of an alkyl halide or a sulfonate ester is a unimolecular process since the rate-determining step is not collision of two molecules but rather slow ionization of the C-Y bond with loss of the leaving group Y. Ionization of an alkyl halide, for example, leads to cation 92 and Y⁻. Carbocation 120 will react with the best available nucleophile, which can be Y⁻ from the ionization process, the solvent or an added nucleophile. The overall substitution reaction is a two-step process (ionization followed by substitution) that is termed $S_N 1$ (a unimolecular nucleophilic substitution).¹³⁵ Electrostatic attraction between the positive carbon of the carbocation and the (-) or (δ -) site of the nucleophile makes the second reaction (coupling) much faster than the initial ionization reaction. For ionization, the term leaving group is a bit of a misnomer since it does not leave but is pulled off, usually by the solvent by solvation and separation of the resulting ions.



 (a) Bateman, L.C.; Hughes, E.D.; Ingold, C.K. J. Chem. Soc. 1940, 960, 1011, (b) Harris, J.M. Prog. Phys. Org. Chem. 1974, 11, 89. The central carbon of carbocation **120** is sp² hybridized and trigonal planar and, as mentioned above, is conveniently viewed as being a trisubstituted carbon atom with an empty p orbital. The relative stability of carbocations is briefly discussed below and again in section 12.2.A in connection with forming carbon-carbon bonds via carbocation intermediates. Since the carbocation has an sp² carbon, **120** has a trigonal planar shape and an attacking nucleophile can approach from either face. This model predicts a racemized substitution product, but this simple model is misleading because stereochemical retention or inversion is often observed in S_N1 reactions. If the initial ionization generates a tight ion pair (represented by **121**), then the leaving group (Y) provides some steric hindrance to the attacking nucleophile and the inverted substitution product (**122**) may predominate, although it is usually not the exclusive product. If the leaving group (Y) can chelate to or otherwise coordinate with the nucleophile, then an ion pair such as **123** may result, and delivery of the nucleophile will be from the same face as the leaving group. Such ion-pairing will lead to a product with retention of configuration (see **124**). Depending on the solvent, a S_N1 reaction may have **120**, **121** or **123** as an intermediate,



but in general the reaction proceeds with significant if not complete racemization at the electrophilic center in acyclic and simple monocyclic compounds. Polycyclic molecules can be an exception, however, since the conformational constraints of the ring system may allow only one face to react with an attacking nucleophile. Adamantyl alcohol (**125**, for example, gives carbocation **126** upon treatment with aqueous HBr. The rigid skeletal structure of **126** limits approach of the nucleophilic bromide to the top of the molecule as shown since one side of the cationic carbon is sterically blocked. As a result, ionization of **125** leads to exclusive formation of **127**.¹³⁶ In general, cationic reactions of this type can be highly stereoselective in substitution reactions if there is steric bias for one face over the other. In the absence of such steric bias, these reactions often show poor to moderate stereoselectivity.



2.6.B.ii. The S_N1 Reaction. The mechanistic rationale described above results from many years of experimental observations about the S_N1 reaction (statements 1-6 below).¹³⁵ In general,

^{136.} Dubowchik, G.M.; Padilla, L.; Edinger, K.; Firestone, R.A. J. Org. Chem. 1996, 61, 4676.

the S_N1 process occurs in those cases where water is present as a solvent or co-solvent, there is a good leaving group, and the substrate is tertiary or secondary. A S_N1 reaction can occur in any polar protic solvent such as methanol, ethanol, or acetic acid, but ionization is much slower in these solvents relative to water because they are not as efficient for the separation of ions (sec. 2.6.B). If ionization is relatively slow, faster reactions (S_N2 or elimination processes) often predominate. In the absence of competing reactions, however, ionization reactions are quite common, and solvolysis of halides in alcohol solvents is quiet common. It is convenient to *assume* that S_N1 reactions occur only in aqueous media, and use this assumption to predict product distributions for a given set of reaction conditions. *As with any assumption, this one fails to accurately predict the products in many cases, but it provides a good working model to begin analyzing reactions*. The ultimate test, of course, is the actual experimental result. The S_N1 process is characterized by the following:

- 1. The rate of reaction with tertiary halides that is much faster than with primary halides,¹³⁷ which is shown in Table 2.11 for reaction of bromoalkanes with potassium iodide in aqueous media.¹³⁷
- 2. The rate equation can be described using only the concentration of the halide and not that of the nucleophile. The rate determining (slow) step is ionization of the C-Br bond and the fast second step does not greatly influence the overall rate. The rate expression is Rate = k [RX] for this unimolecular reaction.¹²⁹
- 3. Reaction with chiral halides proceeds with significant racemization rather than with inversion (see above).
- 4. A cationic intermediate (120) is formed rather than the transition state noted for an $S_N 2$ reaction (see 69).
- **5.** The reaction often proceeds with rearrangement of the carbon skeleton of the organic substrate.
- 6. Unless water is a solvent or co-solvent, the initial ionization reaction is rather slow and may not be competitive with other possible reactions.

Table 2.11. Reaction of Alkyl Halides with Potassium Iodide in Aqueous Media

R–Br	Relative Rate
MeBr	1.0
EtBr	1.0
Me ₂ CHBr	11.6
Me ₃ CBr	1.2×10^{6}

^{137.} Reference 88b, p 43.

A carbocation is the product of ionization, and its stability is critical to the overall rate of the $S_N 1$ process.¹³⁸ A general ranking of carbocations by their relative stability is¹³⁸

$$R_{3}C^{\scriptscriptstyle +} > H_{2}C = CHCH_{2}^{\scriptscriptstyle +} \approx PhCH_{2}^{\scriptscriptstyle +} > R_{2}CH^{\scriptscriptstyle +} > RCH_{2}^{\scriptscriptstyle +} > CH_{3}^{\scriptscriptstyle +}$$

This ranking is based on the electron-releasing inductive properties of the carbon groups attached to the positive center. The three alkyl groups on the tertiary cation release electrons to partially diminish the point charge of the cation, leading to greater stability of the tertiary cation relative to the primary, which has only one electron releasing group. Both allyl and benzyl cations disperse the charge by resonance and are more stable than primary alkyl or secondary alkyl cations. In general, tertiary alkyl cations are probably more stable than a primary allylic cation, although a secondary or tertiary allylic cation will be more stable than a tertiary alkyl. Cation stability is also discussed in section 12.2.A.

With cations ranked according to their relative stability, we then assume that given a choice the more stable cation will be formed in a reaction because it is lower in energy. The addition of HCl to methylenecyclobutane (**128**) illustrates this point, where the final product is 1-chloro-1-methylcyclobutane (**131**), used by Fitjer and Mandelt in a synthesis of cuparene.¹³⁹ The π bond reacts as a base, donating a pair of electrons to the acid (H⁺ = HCl). When the new C–H bond is formed, a carbocation is generated at the other carbon of the π bond, and there are two possible cations, **129** and **130**. The electron-releasing effects of the alkyl groups make the tertiary cation (**129**) more stable than the primary cation (**130**). The reaction will show a preference for **129**, which then traps the nucleophilic chloride (generated by cleavage of HCl after transfer of the proton to the alkene) to give the major product, **131**. The stability of the intermediate cation will largely determine the course of unimolecular reactions.



As mentioned, secondary allylic and secondary benzylic cations are more stable than secondary alkyl cations. This stability is due to participation of the π bond in the ionization process and also by stabilization of the cationic intermediate by resonance. The resonance delocalization in both the allyl cation (132) and the benzylic cation (133) diminishes the net charge at the cationic carbon, making them more stable and easier to form. Although they are more stable, they are highly reactive intermediates and easily react with nucleophiles in a S_N1 reaction. See Figure 12.12.1, sec. 12.2.B, for a more detailed analysis of the relative stability of various

139. Mandelt, K.; Fitjer, L. Synthesis 1998, 1523.

^{138. (}a) Olah, G.A.; Olah, J.A. Carbonium Ions, Vol. 2, Olah, G.A.; Schleyer, P.v.R., Ed. Wiley, New York, 1969, pp 715-782, (b) Richey, J.M. The Chemistry of Alkenes, Vol. 2, Zabicky, J., Ed. Interscience, New York, 1970, p 44.

types of carbocations.



When heteroatoms are attached to a positive carbon, donation of electrons (back donation) to the electron deficient center leads to greater stability, often by resonance delocalization. Two common examples are oxygen-stabilized cations such as **134**, and sulfur-stabilized cations such as **135**. In both cases, back donation from the heteroatom leads to resonance stabilized cations, as shown. Both **134** and **135** are considered to be more stable than a simple tertiary carbocation, but the relative stability really depends on the nature of the groups of the sp² carbon atom. Direct protonation of a carbonyl is the most common method for generating oxostabilized cations such as **134**. Carbonyl protonation leads to the formation of enamines and imines from ketones and aldehydes by reaction with amines,¹⁴⁰ although the key intermediate in both cases is an ammonium ion that functions as the active proton-transfer species (the actual acid catalyst). Another method for generating this cation is by addition of acid to a vinyl ether. Reaction of **136**, for example, gives **137** rather than the tertiary cation **138**, an indication of the greater stability of that oxygen-stabilized cation. Similar results are observed upon protonation of thiocarbonyls or thioenol ethers. As noted above, sec. 2.2.B will provide a more detailed discussion of the stability of heteroatom-stabilized carbocations.



Relief of steric strain influences the rate of $S_N 1$ reactions, although the effect is relatively small. When R is large, the planar carbocation has less steric hindrance than the tetrahedral precursor,

 ⁽a) Hayne, L.W. in *Enamines: Synthesis Structure and Reactions*, Cook, A.G. (Ed.), Marcel Dekker, New York, *1969*, pp. 55-100; (b) Herr, M.E.; Heyl, F.W. *J. Am. Chem. Soc. 1953*, *75*, 5927; (c) *Idem Ibid 1952*, *74*, 3627; (d) Heyl, F.W.; Herr, M.E. *Ibid 1953*, *75*, 1918.

accelerating the ionization process. For example, EtMe₂CCl is ionized to the corresponding carbocation 1.7 times faster than Me₃CCl, Et₂MeCCl is ionized 2.6 times faster, and Et₃CCl 3.0 times faster.^{141g} These ionization rates illustrate that as the steric crowding in the halide increases, the rate of ionization is accelerated.^{141g} This type of crowding, called **back strain** by Brown,^{141d} contributes to the increased rate of ionization observed with hindered halides.^{142d}

In general, $S_N 2$ reactions are faster than $S_N 1$ for primary and secondary halides, and tertiary halides do not give $S_N 2$ reactions but do give $S_N 1$ reactions in protic solvents. In reactions with nucleophiles, primary halides commonly give only $S_N 2$ reactions, and tertiary halides undergo $S_N 1$ processes. Secondary halides give a mixture of bimolecular and unimolecular products in aqueous solvents, and the relative amounts of each type of product are dependent upon the nucleophile, the substrate, and (of course) the ionizing power of the solvent.

2.6.B.iii. Cationic Rearrangements. Reactions that generate cationic intermediates have a potential liability that makes the choice of an $S_N 1$ reaction unsuitable for many syntheses. Carbocations can undergo skeletal rearrangement to give a thermodynamically more stable cation, *prior* to trapping the nucleophile. This means that $k_{rearrangement} > k_{trapping}$ for this type of reaction. If a σ bond is adjacent to the cationic center and parallel to the p-orbital, as illustrated in 139, electron density is donated from the σ -bond. As the electrons in the bond distort toward the positive center, the C-H σ bond weakens and the adjacent orbitals begin to share electron density, as illustrated in 140. As the electrons in the σ bond shift, the atom attached to carbon (H in the case of 139 but it can also be another carbon group) is transferred to the adjacent carbon via transition state 140. As this occurs, a new carbocation is formed as well as a new C-H bond (see 141) to complete the molecular rearrangement (a 1,2-hydride shift). If we examine 139 and 141, the product of the rearrangement is a more stable tertiary cation, generated from a



less stable secondary cation. The driving force for this rearrangement is the energy gained in forming a more stable cation. A tertiary cation is more stable than a secondary by 11-15 kcal mol⁻¹ (46.0-62.7 kJ mol⁻¹) and a secondary cation is more stable than a primary by about the

^{141. (}a) Fry, J.L.; Engler, E.M.; Schleyer, P.v.R. J. Am. Chem. Soc. 1972, 94, 4628; (b) Schleyer, P.v.R.; Nicholas, R.D. Ibid 1961, 83, 182; (c) Tanida, H.; Tsushima, T. Ibid 1970, 92, 3397; (d) Brown, H.C. J. Chem. Soc. 1956, 1248; (e) Brown, H.C.; Borkowski, M. J. Am. Chem. Soc. 1952, 74, 1894. (f) Brown, H.C.; Fletcher, R.S. J. Am. Chem. Soc. 1949, 71, 1845; (g) Harris, J.M.; Wamser, C.C. Fundamentals of Organic Reaction Mechanisms, Wiley, New York, 1976, p118.

^{142. (}a) Fittig, R. Ann. 1860, 114, 54; (b) Collins, C.J. Quart. Rev. 1960, 14, 357; (c) Mundy, B.P.; Otzenberger, R.D. J. Chem. Educ. 1971, 48, 431; (d) Büchi, G.; MacLeod, Jr., W.D.; Padilla, O.J. J. Am. Chem. Soc. 1964, 86, 4438.

same amount.¹⁴³ The substituent can only be transferred (a 1,2-hydride shift for $139 \rightarrow 141$) if the electrons in the σ bond are parallel to the p orbital of the cation.¹⁴⁴ As mentioned above, alkyl groups can move (called 1,2-alkyl shifts) and aryl groups can be transferred (called 1,2-aryl shifts). The energy barrier to transfer of hydrogen is lower than that for alkyl or aryl shifts, but the energy barrier for a 1,2-methyl shift is estimated to be < 5 kcal mol⁻¹ (20.9 kJ mol⁻¹).¹⁴⁵ For the degenerate rearrangement of 142A to 142B, the energy barrier for a 1,2-hydrogen shift was shown to be 3.4 kcal mol⁻¹ (14.2 kJ mol⁻¹).¹⁴⁶ Although the difference in energy between a hydrogen shift and a methyl shift is small, hydrogen will migrate preferentially in virtually all cases. The cationic rearrangements mentioned (1,2-hydride shifts, 1,2-alkyl shifts and 1,2-aryl shifts) all occur with great facility,¹³⁸ to form the more stable carbocation.



The rearrangement just described is not limited to migration of a hydrogen atom. Indeed, many alkyl or even aryl groups (see sec. 12.2.C) can move, as illustrated by the rearrangement of **143** to **144**. In **142**, hydrogen was shifted in preference to a bulkier ethyl group, but in **143** one of the adjacent carbon atoms has three hydrogen atoms and the other carbon has three attached ethyl groups. In this case, migration of a hydrogen from the methyl group would lead to a less stable primary carbocation, and does not occur. To form a more stable tertiary carbocation, one of the ethyl groups must migrate and the 1,2-ethyl shift occurs to give **144**. In general, the smaller substituent migrates preferentially, as in hydrogen versus ethyl in **142**. Rearrangements such as those just described must occur faster than the S_N1-type coupling reaction¹⁴⁷ between the nucleophile and the carbocation. The chemistry of carbocations, including rearrangements, is discussed in more detail in section 12.2.B.

A synthetically useful example of this process is the conversion of **145** to **148**, which involves a 1,2-alkyl shift, and was part of Hwu and Wetzel's synthesis of (–)-solavetivone.¹⁴⁸ The alkyl fragment is actually part of the bicyclic ring system, one arm of the bicyclo[4.4.0]decane ring system. Reaction of the OH unit with the Lewis acid resulted in formation of tertiary cation **146**. A 1,2-alkyl shift gave **147**, where the new cation was stabilized by the well-known

147. Reference 138a, pp 766-778.

 ^{143. (}a) Lossing, F.D.; Semeluk, G.P. Can. J. Chem. 1970, 48, 955; (b) Radom, L.; Pople, J.A.; Schleyer, P.v.R. J. Am. Chem. Soc. 1972, 94, 5935; (c) Arnett, E.M.; Petro, C. Ibid 1978, 100, 5408.

^{144.} Reference 6, pp 427-434.

^{145.} Olah, G.A.; Lukas, J. J. Am. Chem. Soc. 1967, 89, 4739.

^{146. (}a) Saunders, M.; Cline, G.W. J. Am. Chem. Soc. 1990, 112, 3955; (b) Saunders, M.; Kates, M.R. Ibid 1978, 100, 7082.

^{148.} Hwu, J.R.; Wetzel, J.M. J. Org. Chem. 1992, 57, 922.

 β -effect of adjacent silicon of the trimethylsilyl group.¹⁴⁹ Loss of the trimethylsilyl group from **147** gave the final product, spiran **148**.



A second synthetic example illustrates several useful features of cation rearrangements. When **149** (OPiv is a pivaloyl ester) was treated with *p*-toluenesulfonic acid in methanol, protonation occurred at the ether oxygen to generate oxonium ion **150**. Fragmentation of the adjacent C-O bond generated resonance stabilized acyl cation **151**, a more stable cation. There are two reactive hydroxyl groups in **151**, but the acyl cation in **151** can react with one hydroxyl unit to generate a six-membered ring or the other to generate a five-membered ring. The latter mode of attack was favored, and **152** was isolated in 90% yield from this reaction as a part of Danishefsky and co-worker's synthesis of elutherobin.¹⁵⁰



Marshall and co-worker's transformation of the [4.1.0]-bicycloheptane unit in 153 to the

^{149.} See (a) Davidson, A.H.; Fleming, I.; Grayson, J.I.; Pearce, A.; Snowden, R.L.; Warren, S. J. Chem. Soc. Perkin Trans. 1 1977, 550; (b) Fleming, I.; Paterson, I.; Pearce, A. Ibid 1981, 256; (c) Fleming, I.; Patel, S. Tetrahedron Lett. 1981, 22, 2321; (d) Fleming, I.; Michael, J.P. J. Chem. Soc. Chem. Commun. 1978, 245; (e) Roush, W.R.; D'Ambra, T.E. J. Am. Chem. Soc. 1983, 105, 1058.

^{150.} Chen, X.-T.; Bhattacharya, S.K.; Zhou, B.; Gutteridge, C.E.; Pettus, T.R.R.; Danishefsky, S.J. J. Am. Chem. Soc. 1999, 121, 6563.

cycloheptene unit in **155**¹⁵¹ is an example of a reaction that raises mechanistic questions. After protonation of the alcohol unit in **153**, loss of water generated carbocation **154**. A 1,2-alkyl shift to give the cyclopropane unit and trapping of carboxylate would give lactone **155**. Alternatively, nucleophilic attack by the carboxyl oxygen on the cyclopropane ring would open the ring with concomitant expulsion of the leaving group (water) to give **155** without invoking the presence of cation **154**. This latter mechanistic pathway is a synchronous process rather than a stepwise ionic process, and cannot be ruled out based on the formation of the observed product. A tight ion pair in which the ions are not solvent separated offers another reasonable pathway, where the carboxylate anion would react with the cationic center as described above. Additional experimental information about this transformation is required to determine the precise mechanistic pathway. Note that cyclopropylcarbinyl cations such as **154** rapidly open to homoallylic derivatives or cyclobutane compounds,¹⁵² and the cyclopropane ring probably assists in expulsion of the leaving group (in this case an $-OH_2^+$ moiety).



The presence of a free carbocation or the operation of a synchronous mechanism is an important mechanistic consideration when planning any sequence involving cations. Divergent mechanisms can have different influences on the product distribution and stereochemistry of a reaction, and it is important to understand those differences. A detailed kinetic study would presumably determine if a reaction was concerted, stepwise, or a mixture of both. Alternatively, mechanistic studies can be found by examining the literature, or by experimental methods if a synthetic outcome is at all in doubt. Indeed, many synthetic organic chemists regularly publish mechanistically oriented papers. This information will usually solve questions problems with a planned transformation.

2.7. CHARACTERISTICS OF REACTIONS INVOLVING NUCLEOPHILES

It is apparent from section 2.5 that many factors influence the course of nucleophilic reactions, including the nature of the nucleophile, its electron donating capability, the solvent, the substrate

 ⁽a) Marshall, J.A.; Tuller, F.N.; Ellison, R.H. Synth. Commun. 1973, 3, 465. (b) Marshall, J.A.; Ellison, R.H. J. Org. Chem. 1975, 40, 2070; (c) Marshall, J.A.; Ellison, R.H. J. Am. Chem. Soc. 1976, 98, 4312.

⁽a) Julia, M.; Noël, Y.; Guégan, R. Bull. Chim. Soc. France, 1968, 3742; (b) Julia, M.; Noël, Y. Ibid 1968, 3749, 3756; (c) Brady, S.F.; Ilton, M.A.; Johnson, W.S. J. Am. Chem. Soc. 1968, 90, 2882; (d) Poulter, C.D.; Winstein, S. Ibid 1970, 92, 4282; (e) Poulter, C.D.; Friedrich, E.C.; Winstein, S. J. Am. Chem. Soc. 1970, 92, 4274.

and the nature of the leaving group. When substitution (sec. 2.6.A,B) and elimination (sec. 2.9.A,B) in an aliphatic substrate are discussed, these reactions compete if the nucleophiles used are also bases (MeO⁻ for example). The factors mentioned above influence the extent of this competition. It would be very useful to have a list of parameters for such situations that allow one to make predictions. This section will focus on several factors that influence both nucleophilic and elimination reactions. Analysis of these factors lead to key assumptions that allows one to predict the major product in many cases.

2.7.A. The Solvent

A solvent should solubilize all reactants and also absorb excess heat that may be liberated by the reaction. A very important property of a solvent is polarity, which largely determines its ability to solvate and separate ions (solvation). Solvation is an important factor in most nucleophilic reactions, and is very important in acid-base reactions as seen in sec. 2.2. A good measure of the ability to separate ions is the dielectric constant.^{153,154} Table 2.12^{153,154} shows the dielectric constants for several common solvents, where a high dielectric constant means the solution can conduct a current, which is associated with an increase in ion formation (the solvent facilitates ionization).

Protic Solvent	Dielectric Constant		Aprotic Solvent	Dielectric Constant
НОН	78.5	POLAR	H(C=O)NH ₂	109.0
DOD	78.25		DMSO	46.68
EtOH (80% aq)	67		DMF	36.71
HCO ₂ H	58.5		MeCN	37.5
MeOH	32.7		MeNO ₂	35.87
EtOH	24.55		HMPA	30
n-BuOH	17.8		acetone	20.7
NH ₃	16.9		Ac_2O	20.7
t-BuOH	12.47		pyridine	12.4
phenol	9.78		o-dichlorobenzene	9.93
MeNH ₂	9.5		CH_2Cl_2	9.08
MeCO ₂ H	6.15		THF	7.58
			ethyl acrylate	6.02
			chlorobenzene	5.71
			ether	4.34
			CS_2	2.64
			NEt ₃	2.42
			benzene	2.28
			CCl ₄	2.24
			dioxane	2.21
	N	ONPOLA	R hexane	1.88
[Reprinted with permi 3rd ed., Harper and Ro	ssion from Lowry, T.H.; Rio ow, New York, 1987 , pp. 17	chardson, K. 7-181. Cop	S. Mechanism and Theor vright © 1987 by Harper	y in Organic Chemistry, Collins.]

Table 2.12¹⁵⁴ Dielectric Constants and Relative Polarity of Common Organic Solvents

 (a) Reference 6, pp 177-181; (b) Cowdrey, W.A.; Hughes, E.D.; Ingold, C.K.; Masterman, S.; Scott, A.D. J. Chem. Soc. 1937, 1252. For a discussion of solvation energy, see (c) van Bochove, M.A.; Bickelhaupt. F.M. Eur. J. Org. Chem. 2008, 649.

^{153. (}a) Parker, A.J. Quart. Rev. Chem. Soc. 1962, 16, 163, (b) Parker, A.J. Chem. Rev. 1969, 69, 1.

Table 2.12 is further divided into two classes of solvents, those that contain an acidic proton (X–H, **protic**) and those that do not possess an acidic proton (**aprotic**). Within each class, the higher the dielectric constant is associated with the more polar solvent. The essential difference between protic and aprotic solvents is the ability of protic solvents to solvate *both* cations and anions, whereas aprotic solvents efficiently solvate *only* cations. Ionization is favored only when both ions are solvated, allowing them to be separated. The O and the H of the polarized OH unit in the protic solvents water or alcohols are not sterically encumbered, which allows the ^{δ}-O end to solvate cations and the ^{δ +}H end to solvate anions (via hydrogen bonding). The negative dipole of aprotic solvents can solvate cations, but the positive dipole is sterically hindered and anion solvation is poor.

If the solvent is water or contains water, the bimolecular (collision) processes between a neutral substrate and a charged nucleophile (such as nucleophilic acyl addition reactions and nucleophilic displacement with alkyl halides) are generally slow due to solvation effects. Water is an excellent solvent for the solvation and separation of ions, however, so unimolecular processes (which involve ionization to carbocations, see sec. 2.6.B.i) may be competitive. If the solvent is not water, ionization is much slower. Ionization certainly occurs in alcohols or solvents like acetic acid, but the process is so slow that other reactions may occur faster. Based on this observation, we can *assume* that ionization (unimolecular reactions) will be competitive in water, but not in other solvents, leading to the assumption that bimolecular reactions should dominate in solvents other than water. This statement is clearly an *assumption*, and it is not entirely correct since ionization can occur in ethanol, acetic acid, and so on, but the assumption is remarkably accurate in many simple reactions and it allows one to begin making predictions about nucleophilic reactions. Even if those predictions are shown experimentally to be incorrect, one begins to understand the factors that are important to each reaction. In those cases where the assumption fails and the products are different from those predicted, the analysis will lead to a better understanding of the overall process. Remember, however, that the various devices used in this section to predict the major product are *assumptions*.

The solvation effect of water is based on its ability to surround the nucleophilic and electrophilic centers (by hydrogen bonding to the electrophilic H or the nucleophilic O: HO–H----X⁻ and H₂O----X⁺), making collision more difficult in a bimolecular process. For ionization to compete with bimolecular processes, the counterion should be a weak nucleophile and/or a weak base in most cases. If the counterion is too basic, it can induce elimination that can be faster than ionization. If the counterion is too nucleophilic, bimolecular substitution processes will be faster.

In an ionization reaction involving water, the $^{\delta+}$ C and the X^{$\delta-$} groups coordinate with the oxygen and proton of water, respectively. Such coordination "pulls" the C–X bond, thus increasing the bond polarity, allowing greater solvation by the water. Solvation of the polarized atoms eventually leads to separation of the developing charges, which accelerates the ionization process and stabilizes the ion products. The net result is ionization of the C–X bond into a carbocation and the X⁻ anion, both solvated by water. In an aprotic solvent such as diethyl ether, solvation of the cation is possible but the anion is not solvated very well. In practical terms, the solvent does *not* help to pull the leaving group away in the rate determining step so ionization is much slower and generally not competitive with bimolecular processes. Even in protic solvents such as ethanol, the dielectric is so small that charge separation is inefficient, again slowing the rate determining ionization step in a unimolecular reaction.

In nucleophilic substitution reactions of alkyl halides, a pentacoordinate transition state (see **69**) is formed at the midpoint of this bimolecular process. No intermediate has ever been observed. If water is the solvent, separating charges will hinder formation of the transition state, which will slow both bimolecular substitution and elimination reactions. A large number of nucleophiles and bases are ionic, and they will be solvated by water. The solvated nucleophile must penetrate its own solvent sheath as well as any solvation sphere associated with the electrophile to reach the carbon for collision in a bimolecular process, which effectively reduces its nucleophilicity. Nucleophilic strength is, therefore, dependent on the solvent. Aprotic solvents solvate cations but the nucleophile is not well solvated. Therefore, the nucleophile has virtually no solvent sheath and can approach the electrophilic center with greater ease, effectively increasing the nucleophilicity. Using an aprotic solvent therefore allows the maximum rate possible for the bimolecular process. In all cases, the more polar the solvent, protic or aprotic, the more pronounced will be the solvation effect. Solvation will influence the height of reaction barriers, often due to changes in the solvation energy of the transition state.^{154c} "Variations in ΔG_{Esolv} (transition state) are larger than those in ΔG_{Esolv} (reactants)."

2.7.B The Substrate

Bimolecular processes in general are dependent on the nature of the substrate (the molecule containing the electrophilic center). Bimolecular processes generally dominate reactions of primary alkyl halides. The low lying transition state available for bimolecular substitution (secs. 2.6.A,B) is responsible for this observation, combined with the high energy required to form a primary cation (sec. 2.6.B.i). Substitution reactions tend to be faster than elimination for primary halides, even in protic solvents. Exceptions occur when a very hindered base (or nucleophile) such as DBN or DBU is used (**26** and **21**, respectively), since approach of those reagents to the carbon bearing the leaving group is difficult.

In reactions of tertiary halides, unimolecular processes dominate in protic solvents (especially water and aqueous solvents) where substitution is usually faster than elimination. A carbocation is formed in the ionization process and substitution involves nucleophilic attack directly at a positive carbon, whereas elimination involves removal of an acidic hydrogen two bonds removed from the positive carbon. Clearly, a nucleophilic species is strongly attracted to the most positive center and that should lead to the major product. In aprotic solvents, bimolecular substitution is not observed for tertiary halides due to the high energy required to form the

pentacoordinate transition state (sec. 2.6.A.i). Under conditions that favor bimolecular reactions, and in the presence of a suitable base, elimination is the dominant process.

For secondary halides in aqueous solvents, unimolecular and bimolecular processes compete, and the result is usually a mixture of products. With a strong base and a protic solvent other than water, bimolecular elimination is usually faster than substitution, although this is only an assumption and accurate predictions can be difficult with secondary substrates. In polar aprotic solvents, bimolecular processes are usually faster. If a strong base is present and a protic solvent is used, bimolecular elimination is usually preferred to bimolecular substitution, but this is another assumption. These assumptions can be summarized by saying that elimination is preferred in protic solvents and substitution in aprotic solvents, for secondary halides and sulfonate esters. If ethanol is used as a solvent and sodium ethoxide is a nucleophilic base, Table 2.13 shows the competition between bimolecular substitution (S_N 2) and bimolecular elimination (E2) for a series of alkyl bromides. The preference for E2 reactions of secondary and tertiary halides in this protic solvent is clearly shown.

Table 2.13.¹⁵⁵ Relative Rates of Substitution vs. Elimination for Alkyl Bromides

Halide	$k (S_N 2)$	k (E2)	% Alkene
EtBr	172	2.6	0.9
n-PrBr	54.7	5.3	8.9
<i>i</i> -PrBr	0.058	0.237	80.3
t-BuBr	0.1	4.17	97
[Reprinted with permission from Hine, J. Physical Organic Chemistry, 2nd ed., McGraw-Hill New York 1962 p. 203 Copyright 1962 McGraw-Hill]			

2.7.C. The Nucleophile-Base

In a bimolecular process, the stronger the nucleophile, the greater the attraction for $^{\delta+}$ C, which is favored in aprotic solvents. When the nucleophile is also a base, the rate of elimination will increase relative to substitution as base strength increases. In general, high nucleophilicity and/or high basicity leads to a competition between S_N2 and E2. If the attacking species is a strong nucleophile but a weak base, the reaction will proceed almost entirely by S_N2 when primary and secondary substrates are involved, but tertiary substrates show elimination or no reaction at all depending on the strength of the base. With low nucleophilicity, high basicity species, E2 dominates for tertiary and secondary substrates. Even primary halides can undergo elimination with a nonnucleophilic base such as DBN (**26**) or DBU (**21**).

For unimolecular reactions, unimolecular substitution (S_N 1, sec. 2.6.B.ii) is favored with strong, non-basic nucleophiles in aqueous media. Unimolecular elimination (E1, sec. 2.9.B) processes are favored with bases of weak to moderate strength that are also poor nucleophiles. Such bases

^{155.} Hine, J. Physical Organic Chemistry, 2nd Ed. McGraw-Hill, New York, 1962, p 203.

include the hydrogen sulfate anion and the perchlorate anion, which are resonance stabilized and very poor nucleophiles. In general, the S_N1 reaction is faster than the E1 reaction since the cationic carbon is most strongly attracted to the electron rich center, but this assumption is complicated by the fact that the S_N1 product is often unstable and/or difficult to isolate. The hydrogen sulfate or perchlorate S_N1 products are classical examples of unstable substitution products, and in such a case, the E1 process may lead to the major product.

2.7.D. Concentration of the Reacting Species

For bimolecular processes, the rate of reaction is given by the expression: Rate = k [nucleophile or base] [RX], where k is the rate constant. Increasing the concentration of the nucleophile, halide, or base leads to an increase in rate. Decreasing the concentration will decrease the rate. To ensure a rapid and complete reaction, an excess of base or nucleophile is often used.

For unimolecular processes, the rate of the reaction is given by Rate = $k_1 [RX] + k_2$ [nucleophile or base], because this is a two-step process, ionization followed by substitution. The two steps (two reactions) are (1) ionization of the substrate to form a cation (rate = $k_1 [RX]$) and (2) reaction of the cation with the nucleophile or base to produce the product (rate = $k_2 [R^+]$ [nucleophile or base]). For the unimolecular reaction, the overall rate is actually shown to be Rate = k [RX], where the observed rate constant (k) is consistent with the first process (k_1) being very slow and the second (k_2) being so fast that changes in k_2 have little or no effect. Ionization is indeed the slow step and trapping the resulting carbocation with a nucleophile is very fast, so ionization is the rate-determining step in the reaction. An increase or decrease in the concentration of nucleophile or base, therefore, has only a minor effect on the overall rate of the reaction in most cases. Unimolecular reactions are commonly done in an aqueous solvent mixture (aq THF, aq acetone, etc.) with as a high a concentration of substrate and nucleophile or base as is possible in the aqueous medium.

2.7.E. The Leaving Group

A leaving group (X) is the atom or group of atoms displaced in a substitution or elimination reaction. A good leaving group should have a relatively weak and polarized C-X bond. After departure, X should be a very stable ion, or a stable neutral molecule such as water. If this ion or molecule can be effectively solvated, its leaving group ability is enhanced. In general, gegenions derived from strong acids are good leaving groups and those derived from weak acids are poor leaving groups. Typical good leaving groups that generate ions after their departure are Br, I, OTs, OMs, and Cl and typical poor leaving groups are OAc, OH and NH₂, although acetate is a common leaving group for many reactions and it is significantly better than hydroxyl or amino. What this really says is that more vigorous conditions are required for OAc to leave than would be required for Br to leave. In general, this statement is true. Although "OH and "NH₂ are poor leaving groups, alcohols can be protonated to generate

oxonium ions, where water is a good leaving group. Similarly, amines can be protonated to form an ammonium ion, and ammonia can be a good leaving group.

Halides are probably the most common leaving groups. A general order of leaving group ability for halides is I > Br > Cl >>> F. Large atoms such as iodide form a C–I unit, which has a longer bond than C–F so one expects iodide to be a better leaving group than fluoride. The longer bond is generally weaker due to less electron density between the nuclei, and easier to break (it is actually displaced by the nucleophile). After the halide departs, the larger iodide is better solvated by the solvent, diminishing the net charge of the ion and making it more stable, which assists the overall reaction. The role of iodide as a leaving group is complicated by the fact that it is a better nucleophile than fluoride (sec. 2.6.A.i). If an excess of iodide is used in a nucleophilic displacement reaction with a chiral allylic iodide, the iodide functions as both a leaving group and a nucleophile, and iodide displaces iodide with successive $S_N 2$ inversions leading to racemic product. The less basic the group, the more easily it departs. Table 2.14¹⁵⁶ provides a limited rate comparison of leaving group ability in a specific $S_N 2$ reaction.

Et-X + EtO ⁻ -	\rightarrow Et-O-Et + X ⁻
Х	Relative Rate (k _x /k _{Br})
Cl	0.0024
Br	2.0
Ι	2.9
OTs	3.6
[Reprinted with permission from Lowry, <i>Chemistry, 3rd ed.</i> , Harper and Row, Net	T.H.; Richardson, K.S. Mechanism and Theory in Organic w York, 1987, pp. 374. Copyright © 1987 by Harper Collins.]

 Table 2.14. Leaving group ability in the reaction of haloethanes and ethoxide:

The problems of nucleophilic leaving groups such as iodide (see above) could be alleviated if the leaving group were not nucleophilic. Tosylate $[-OSO_2-C_6H_4(4-Me)]$ and mesylate $(-OSO_2-CH_3)$ groups are derived from sulfonic acids and they are good leaving groups. However, the resonance-stabilized anion (RSO₃⁻) has a diffuse charge and is a poor nucleophile. Indeed, sulfonate esters possess several qualities of a good leaving group: (1) resonance stabilization of the departed ion, (2) relief of steric strain upon leaving due to the bulk of the group, and (3) the relative weakness of the C-O (sulfonate) bond

Groups involving second-row elements are usually better leaving groups than comparable first row element groups. Charged species (which generate neutrals after departure) are better leaving groups than neutral leaving groups (which generate charged species after departure).

These preferences are illustrated by $RS^- > RO^-$ and $R_2O^+ >>>> RO^-$.

In general, good leaving groups are large, of low nucleophilicity, more stable after departure,

^{156.} Reference 6, p 374.

and of low electronegativity. High polarizability with large atoms such as iodide or sulfur is usually associated with weaker bonds and better leaving group ability. Poor leaving groups are small, very nucleophilic, and highly electronegative.

2.8. SUBSTITUTION BY HALOGEN

Halogen can be introduced into a molecule is several ways, including substitution of one halogen atom for another. An important method involves replacement of the OH unit of an alcohol with halogen. The hydrogen atom of an alkyl fragment, particularly an allylic or benzylic fragment can be replaced with halogen by a free-radical mechanism. Both of these transformations will be examined in this section.

2.8.A. Halogenation of Alcohols

The reaction of a tertiary alcohol with HBr or HCl to give a halide via a carbocation intermediate is a general reaction in which alcohols react with mineral acids (HCl, HBr, and HI) to give the corresponding alkyl halide.¹⁵⁷ We can explain the process by a simple example in which 1-methyl-1-cyclohexanol (**156**) reacts with HBr to initially give oxonium ion **157**, which loses H_2O to produce tertiary methylcyclohexyl cation **158**. This cation traps the gegenion of the acid (Br⁻ in this case) to give **159**.



Reaction of 1-butanol with HBr also gives the expected primary halide but the reaction follows an S_N2 mechanism, with bromide displacing ${}^+OH_2$ in the sequence $160 \rightarrow 161 \rightarrow 162$. The high energy barrier for ionization of 161 to the relatively unstable primary cation, coupled with the low energy demands to the S_N2 transition state lead to this preference. For secondary alcohols, both mechanisms can operate simultaneously and competitively. In aqueous media, the cationic mechanism usually dominates for secondary substrates, but if no solvent is used (neat) or if the reaction occurs in aprotic solvents the S_N2 mechanism dominates. The mechanism obviously depends on the specific substrate and the reagents used, as well as on the reaction conditions. As a functional group exchange, however, reaction of primary, secondary or tertiary alcohols with HBr or HCl is an excellent method for the preparation of alkyl bromides or chlorides.

^{157.} For examples see Ref. 3, pp 689-696.



Several halogenating reagents other than HBr, HCl, or HI have been discovered that convert alcohols to halides,¹⁵⁷ usually sulfur or phosphorus halides or oxyhalides. Two of the most common are thionyl chloride (SOCl₂) and thionyl bromide (SOBr₂). Thionyl chloride reacts with an alcohol to form an alkyl chlorosulfite (**163**).

Subsequent loss of CISO_2^- generates a cation that dissociates to a tight ion pair (represented by **164**), and chloride is transferred to carbon intramolecularly with retention of configuration.¹⁵⁸ Chlorine is unable to approach the rear of the cation and the ion pair does not dissociate sufficiently to allow a S_N1-type reaction. In this case, 2(*R*)-butanol was converted to 2(*R*)-chlorobutane. The mechanistic designator for this process is (Substitution Nucleophilic Internal), S_Ni, and requires that the leaving group possess an atom capable of being transferred to the carbon substrate.¹⁵⁹ When primary alcohols are treated with thionyl chloride, the chloride is usually formed inexcellent yield. An example, taken from Chai and co-worker's synthesis of hybocarpone,¹⁶⁰ reacted benzylic alcohol **165** with thionyl chloride to give a 96% yield of benzylic chloride **166**. Subsequent reaction with KCN in DMSO gave **167** in 99% yield, in a classical S_N2 reaction (see 2.6.A.i).



If a basic amine such as pyridine is added to this reaction mixture, the stereochemistry of the final product is different. Initial reaction with alcohol **168** gives **169**, but pyridine (or another basic tertiary amine) reacts with the HCl by-product to give pyridinium hydrochloride (see

^{158. (}a) Lee, C.C.; Clayton, J.W.; Lee, D.G.; Finlayson, A.J. *Tetrahedron* 1962, 18, 1395; (b) Lee, C.C.; Finlayson, A.J. *Can. J. Chem.* 1961, 39, 260.

^{159. (}a) Reference 7, p 420; (b) Lewis, E.S.; Boozer, C.E. J. Am. Chem. Soc. 1952, 74, 308.

^{160.} Chai, C.L.L.; Elix, J.A.; Moore, F.K.E. J. Org. Chem. 2006, 71, 992.

170). The nucleophilic chloride ion is now in solution rather than being lost as HCl, and it displaces the chlorosulfite unit in an $S_N 2$ reaction that gives alkyl chloride **171** with inversion of configuration. Reaction of an alcohol with thionyl chloride and pyridine is called the **Darzens' procedure**.¹⁶¹ A modification that improves the stereoselectivity premixes the alcohol with thionyl chloride and pyridine, and the resulting sulfinate is treated with thionyl bromide.¹⁶² Thionyl bromide converts alcohols to the bromide,¹⁶³ but the extent of inversion or retention is not as clean as with thionyl chloride. Thionyl chloride is a common reagent for the R–OH \rightarrow R–Cl transformation. An acid by-product is produced, however, and sensitive systems (particularly allylic alcohols) may be subject to acid catalyzed rearrangements and side reactions.



Phosphorus halides give the ROH \rightarrow RX transformation for primary, secondary, and tertiary alcohols. The most common reagents are phosphorus trichloride (PCl₃), phosphorus pentachloride (PCl₅), phosphorus oxychloride (phosphoryl chloride, POCl₃), phosphorus tribromide (PBr₃), and phosphorus pentabromide (PBr₅). The chloride reagents give less rearrangement in reactions with alcohols than is observed with HBr or HI. Some rearrangement is commonly observed with secondary alcohols, even with the phosphorus reagents.

Phosphorus trichloride is commonly used for the preparation of acid chlorides¹⁶⁴ but less often for the conversion of alcohols to chlorides because other reagents are more practical. This contrasts with phosphorus tribromide, which is a common reagent for conversion of alcohols to bromides.¹⁶⁵ A typical example is taken from a synthesis of the C(1)–C(19) fragment of tetrafibricin by Roush and Lira,¹⁶⁶ in which the reaction of allylic alcohol **172** with PBr₃ and pyridine gave bromide **173** in good yield. An alternative and convenient method for converting alcohol to bromides uses a mixture of carbon tetrabromide and triphenylphosphine. An example is the conversion of **174** to **175** in 96% yield, taken from Jamison and Woodin's synthesis of pumiliotoxins 209F and 251D.¹⁶⁷ Triphenylphosphine and *N*-chlorosuccinimide (NCS, see sec. 2.8.B) converts allylic alcohols to allylic chlorides.¹⁶⁸ Conversion of an alcohol to a mesylate

165. Fieser, L.F.; Fieser, M. Reagents for Organic Synthesis Vol. 1, Wiley, New York, 1967, p 873.

^{161.} Darzens, G. Compt. Rend. 1911, 152, 1601.

^{162.} Frazer, M.J.; Gerrard, W.; Machell, G.; Shepherd, B.D. Chem. Ind. 1954, 931.

^{163.} Elderfield, R.C.; Kremer, C.B.; Kupchan, S.M.; Birstein, O.; Cortes, G. J. Am. Chem. Soc. 1947, 69, 1258.

^{164.} Allen, C.F.H.; Barker, W.E. Org. Synth. Coll. Vol. 2 1943, 156.

^{166.} Lira, R.; Roush, W.R. Org. Lett. 2007, 9, 533.

^{167.} Woodin, K.S.; Jamison, T.F. J. Org. Chem. 2007, 72, 7451.

^{168.} For an example from a synthesis see Lan, J.; Li, J.; Liu, Z.; Li, Y.; Chan, A.S.C. *Tetrahedron: Asymmetry* **1999**, *10*, 1877.

followed by treatment with LiBr is a mild method for preparing bromides,¹⁶⁹ and treatment with LiCl gives the chloride.¹⁷⁰ A mixture of carbon tetrachloride and hexamethylphosphorus triamide (HMPT) has been used to convert alcohols to chlorides.¹⁷¹



The bromination method mentioned above using triphenylphosphine and either CBr_4 or elemental bromine is a particularly mild method for this transformation. Cyclopropylcarbinyl alcohols are acid sensitive substrates, for example, usually giving ring-opening products or cyclobutane derivatives on treatment with acid (see above).^{159,172} When **176** was treated with PPh₃ and bromine, however, a 79% yield of **177** was obtained.^{173,174} It was essential that the bromide-triphenylphosphine-alcohol complex be heated in order to generate this bromide, since mixing the reagents without heating gave only starting material.¹⁷³



Phosphorus pentachloride is commonly used for the preparation of acid chlorides,¹⁷⁵ along with thionyl chloride.¹⁷⁶ Bromination of aromatic rings has been reported using POBr₃ in DMF, in the conversion of **178** to **179** in DeShong and McElroy's synthesis of the CD-ring of streptonigrin.¹⁷⁷

- 172. Descoins, C.; Samain, D. Tetrahedron Lett. 1976, 745.
- 173. Hrubiec, R.T.; Smith, M.B. J. Org. Chem. 1984, 49, 431.
- (a) Kirmse, W.; Kapps, M.; Hager, R.B. Chem. Ber., 1966, 99, 2855; (b) Wiley, G.A.; Hershkowitz, R.L.; Rein, B.M.; Chung, B.C. J. Am. Chem. Soc. 1964, 86, 964.

For examples from syntheses, see (a) Clive, D.L.J.; Hisaindee, J. Org. Chem. 2000, 65, 4923; (b) Huang, A.X.; Xiong, Z.; Corey, E.J. J. Am. Chem. Soc. 1999, 121, 9999.

^{170.} Smith III, A.B.; Wan, Z. J. Org. Chem. 2000, 65, 3738.

^{171.} For an example taken from a synthesis of (+)-australine, see White, J.D.; Hrnciar, P. J. Org. Chem. 2000, 65, 9129.

^{175.} Reference 165, p 866.

^{176.} For an example from a synthesis see Mori, K.; Tashiro, T.; Sano, S. Tetrahedron Lett. 2000, 41, 5243.

^{177.} McElroy, W.T.; DeShong, P. *Tetrahedron* 2006, 62, 7155. For the use of PBr₅ in this type of reaction, see Kaslow, C.E.; Marsh, M.M. J. Org. Chem. 1947, 12, 456.



In combination with pyridine, phosphoryl chloride (POCl₃) reacts with alcohols to form an intermediate that undergoes elimination to give an alkene (see sec. 2.9.A for elimination reactions). The elimination generally gives the best results with tertiary alcohols, although secondary alcohols work as well. The secondary alcohol unit **180** was dehydrated to give **181** by treatment with POCl₃ and pyridine, albeit in only 26% yield in Basabe and co-workers enantioselective synthesis of luffolide.¹⁷⁸ A mixture of thionyl chloride and pyridine can also lead to elimination.¹⁷⁹ Substitution by chloride ion sometimes competes with elimination when secondary alcohols are substrates. Treatment of alcohol **182** with POCl₃ and pyridine, for example, gave chloride **183** rather than the conjugated ene-yne.¹⁸⁰ As with other halogenating agents, primary alcohols react to give mainly the substitution product, the alkyl halide. Phosphorus pentabromide can be used with secondary alcohols in place of PBr₃ since much less rearrangement occurs.¹⁷⁵



Although most phosphorus chlorides and bromides are commercially available, it is sometimes necessary to prepare the appropriate reagent as it is needed. The phosphorus iodides have poor shelf lives (they are unstable and decompose under mild conditions) and are usually prepared *in situ*, or immediately prior to use by reaction of red phosphorus with iodine. Using P and I₂ is a common method for the conversion of aliphatic alcohols to aliphatic iodides. An example is the conversion of cetyl alcohol (**184**) to cetyl iodide (**185**) in 85% yield.¹⁸¹ Another popular method is illustrated by treatment of **186** with triphenylphosphine, iodine, and imidazole. In

^{178.} Basabe, P.; Delgado, S.; Marcos, I.S.; Diez, D.; Diego, A.; De Roman, M.; Urones, J.G. J. Org. Chem. 2005, 70, 9480

^{179.} For an example taken from a synthesis of (–)-cacospongionolide F, see Demeke, D.; Forsyth, C.J. *Org. Lett.* 2003, 5, 991.

^{180.} Truscheit, E.; Eiter, K. Liebigs Ann. Chem. 1962, 658, 65.

^{181. (}a) Reference 165, p 862; (b) Hartman, W.W.; Byers, J.R.; Dickey, J.B. Org. Synth. Coll. Vol. 2 1943, 322.

this example, taken from Marshall and Schaaf's synthesis of leptofuranin D,¹⁸² the primary alcohol unit was converted to iodide **187** in 94% yield. Phosphorus bromides can also be prepared from phosphorus and bromine. Reaction of 1,2,3-propanetriol with red phosphorus and bromine, for example, gave 1,3-dibromo-2-propanol.¹⁷⁷



The **Finkelstein reaction** is highly useful for converting various halides into an iodide¹⁸³ in which an alkyl chloride, bromide, mesylate, or tosylate is treated with NaI or KI to produce alkyl iodides via an S_N2 reaction. In a synthesis of mosin B,¹⁸⁴ Tanaka, Monden, and co-workers converted tosylate **188** to iodide **189** in 79% yield with sodium iodide in acetone. This reaction is required when a better leaving group is required for a given transformation. Since alkyl iodides are known to decompose upon long standing, the Finkelstein reaction allows the iodide to be generated *in situ* and used immediately.



When allylic alcohols are subjected to acidic conditions, formation of the allyl cation can lead to regioselectivity problems as well as polyalkylation or S_N2' reaction by-products. Most of the halogenating reagents described can give deleterious side reactions. Such problems can be circumvented or alleviated by using a different type of halogenating reagent. Magid showed that allylic alcohols such as **190** are converted to allylic chloride **191** by a mixture of triphenylphosphine (PPh₃) and hexachloroacetone that gives chlorotriphenylphosphonium

^{182.} Marshall, J.A.; Schaaf, G.M. J. Org. Chem. 2003, 68, 7428. Alcohols are converted to iodides using (PhO)₃P⁺CH₃I⁻ in DMF: see Su, Q.; Dakin, LA.; Panek, J.S. J. Org. Chem. 2007, 72, 2 in a synthesis of leucascandrolide A.

^{183. (}a) Finkelstein, H. Berichte 1910, 43, 1528; (b) Ingold, C.K. Structure and Mechanism in Organic Chemistry, 2nd Ed. Cornell Univ. Press, London, 1969, p 435; (c) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-31.

Maezaki, N.; Kojima, N.; Sakamoto, A.; Tominaga, H.; Iwata, C.; Tanaka, T.; Monden, M.; Damdinsuren, B.; Nakamori, S. Chem. Eur. J. 2003, 9, 390.

chloride (Cl–PPh₃⁺Cl⁻),¹⁸⁵ the chlorinating species. The reaction of triphenylphosphine with bromine or carbon tetrabromide (CBr₄) similarly converts an alcohol into the corresponding bromide, as we have seen above.



There are other functional group transformations that give alkyl halides. A classical transformation converts carboxylates to alkyl bromides (C-CO₂⁻ \circledast C-Br). This transformation is called the **Hunsdiecker reaction**¹⁸⁶ (it has also been called the **Borodin reaction**),¹⁸⁷ and it is most useful for the preparation of secondary halides. Note that Borodin was a noted composer of classical music¹⁸⁸ as well as a chemist. The silver salt of a carboxylic acid is heated with bromine to give the bromide via decarboxylation. An example is conversion of the silver salt of cyclohexane carboxylic acid (**192**) to bromocyclohexane.¹⁸⁹ In a different process, phosphorus and bromine react with acids in the **Hell-Volhard-Zelinsky reaction**.¹⁹⁰ An example is the conversion of cyclopropanecarboxylic acid to the α -bromo acid bromide **193**, which was reacted with 4-aminopyridine **194** to give **195** in Storey and Ladwa's synthesis of 5-azaoxindoles.¹⁹⁰



^{185. (}a) Magid, R.M.; Fruchey, O.S.; Johnson, W.L.; Allen, T.G. J. Org. Chem. 1979, 44, 359; (b) Magid, R.M.; Fruchey, O.S. J. Am. Chem. Soc. 1977, 99, 8368.

⁽a) Hunsdiecker, H.; Hunsdiecker, Cl. Berichte 1942, 75, 291; (b) Johnson, R.G.; Ingham, R.K. Chem. Rev. 1956, 56, 219; (c) Wilson, C.V. Org. React. 1957, 9, 332 (see p 341); (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-47. For a microwavae-promoted version see Bazin, M.-A.; El Kihel, L.; Lancelot, J.-C.; Rault, S. Tetrahedron Lett. 2007, 48, 4347.

^{187.} Borodine, A. Annalen 1861, 119, 121.

See the biography by (a) Abraham, G.; Seroff, V.I. *The Mighty Five* (1948); See also, (b) Zetlin, M.O. *The Five* (tr. 1959).

^{189. (}a) Eliel, E.L.; Haber, R.G. J. Org. Chem. 1959, 24, 143; (b) Marvell, E.N.; Sexton, H., Ibid 1964, 29, 2919.

^{190. (}a) Hell, C. *Berichte* 1881, 14, 891; (b) Volhard, J. *Annalen* 1887, 242, 141; (c) Zelinsky, N. *Berichte* 1887, 20, 2026; (d) Watson, H.B. *Chem. Rev.* 1930, 7, 180; (e) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-42; (e) Storey, J.M.D.; Ladwa, M.M. *Tetrahedron Lett.* 2006, 47, 381.

2.8.B. ALLYLIC AND BENZYLIC HALOGENATION

Bromine or chlorine can be introduced into a molecule by processes that generate radical intermediates.¹⁹¹ The reaction of bromine or chlorine with allylic and benzylic compounds, in the presence of heat, light or radical initiators (secs. 13.3, 13.4) leads to resonance stabilized free radicals that react with additional bromine or chlorine to give the corresponding halide. Addition of diatomic bromine to **196** (in the presence benzoyl peroxide and photochemical initiation) gave benzylic bromide **197** in high yield in a synthesis of indole alkaloids.¹⁹² This reaction is just another example of the well-known free-radical substitution reaction of alkanes with chorine or bromine in the presence of light (*h*v) or heat. The resonance stability of an allylic or a benzylic radical is a significant contributor to the benzylic or allylic selectivity. In non-allylic or benzylic systems, radical chlorination of alkanes by chlorine is unselective, converting virtually all C–H bonds in the molecule to C–C1. Bromination, on the other hand, is more selective in such systems, showing a great propensity to react with tertiary positions (tertiary C–H) to give tertiary bromides, as in the conversion of 2-methylpentane to **198**. Chlorination.



Halogenation of allylic and benzylic C–H moieties is more convenient using the readily available *N*-bromosuccinimide (NBS, **199**) or *N*-chlorosuccinimide (NCS, **200**) with radical initiators, heat and/or light,¹⁹³ in what is called the **Wohl-Ziegler reaction**.^{193f,g,h,194} Reactions with NBS are commonly carried out in refluxing carbon tetrachloride, with addition of a catalytic amount of radical initiator [such as *azobis*-isobutyronitrile (AIBN) or benzoyl peroxide, sec. 13.3], or with an incandescent lamp held close to the reaction. Heating AIBN leads to homolytic cleavage and formation of a cyano radical (Me₂C·–CN), which initiates the radical chain process (sec. 13.3). This chain process generates the allylic (or benzylic) radical that reacts with bromine (or additional NBS) to give the allylic or benzylic bromide product and another radical chain carrier.¹⁹³ Reaction with NCS proceeds by a similar mechanism. A synthetic example, taken

^{191.} For examples see Ref. 3, pp 611-615.

^{192.} Söderberg, B.C.; Chisnell, A.C.; O'Neil, S.N.; Shriver, J.A. J. Org. Chem. 1999, 64, 9731.

^{193. (}a) Goldfinger, P.; Gosselain, P.A.; Martin, R.H. Nature (London) 1951, 168, 30; (b) McGrath, B.P.; Tedder, J.M. Proc. Chem. Soc. 1961, 80; (c) Pearson, R.E.; Martin, J.C. J. Am. Chem. Soc. 1963, 85, 354; (d) Russell, G.G.; DeBoer, C.; Desmond, K.M. Ibid 1963, 85, 365; (e) Walling, C.; Rieger, A.L.; Tanner, D.D. Ibid 1963, 85, 3129; (f) Wohl, A. Berichte 1919, 52, 51; (g) Ziegler, K. Späth, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. Annalen 1942, 551, 80; (h) Djerassi, C. Chem. Rev. 1948, 43, 271.

^{194.} The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-102.

from Goosen and Melzer's synthesis of valsartan,¹⁹⁵ in which the benzylic methyl group in **201** was converted to the bromomethyl unit in **202** by reaction with **199** and AIBN.



Ketones that have an enolizable hydrogen can be halogenated at the α position (the carbon adjacent to the carbonyl) with bromine, chlorine, NBS, or NCS.¹⁹⁶ The reaction probably proceeds via addition of X₂ to the enol form of the carbonyl (secs. 9.2.A, 9.8.A). Elimination of HX from the addition product generates a new enol, which tautomerizes to the α -haloketone.¹⁹⁶ Reaction of cyclohexanone with bromine, for example, gives 2-bromocyclohexanone (**204**) and reaction with NCS (**200**) gives 2-chlorocyclohexanone (**203**).



Halogenation of carbonyl compounds is often accompanied by secondary reactions. The initially formed α -halo carbonyl can react with another equivalent of halogen to give the α,α -dihalocarbonyl. In the bromination of cyclohexanone, 2,2,-dibromocyclohexanone (**205**) was also produced. Usually the mono-halogenated product predominates with ketones, but this depends on the substrate and the reaction conditions. Halogenation of lactams using this method often gives a α,α -dihalide. 2-Pyrrolidinone, for example, reacts with NCS or PCl₅, to give a mixture of 3-chloro- and 3,3-dichloro-2-pyrrolidinone.¹⁹⁷ When phosphorus halides are used the dichloride is usually the major product, but the monochloride can be formed in reasonable yield using NCS.

In unsymmetrical ketones, halogenation usually occurs at the more highly substituted α position, but regioselectivity can be a problem. Heating an unsymmetrical ketone with *tert*-butyl bromide and DMSO at 65°C is a mild and selective solution to the problem,¹⁹⁸ usually giving the more substituted bromide. Another problem in halogenation reactions of carbonyls is elimination (note that POCl₃ is produced as a side product when PCl₅ is used). When

^{195.} Goosen, L.L.; Melzer, B. J. Org. Chem. 2007, 72, 7473.

^{196.} Catch, J.R.; Hey, D.H.; Jones, E.R.H.; Wilson, W. J. Chem. Soc. 1948, 276.

^{197.} Elberling, J.A.; Nagasawa, H.T. J. Heterocyclic Chem. 1972, 9, 411.

^{198.} Armani, E.; Dossena, A.; Marchelli, R.; Casnati, G. Tetrahedron 1984, 40, 2035.
cyclopentanone reacted with PCl₅, for example, 1-chlorocyclopentene was the major product, via elimination, but 1,1-dichlorocyclopentane was also formed by addition of chloride ion to the α -chloro-carbocation.¹⁹⁹ Similarly, cyclohexanone gave 1-chlorocyclohexene (**206**).²⁰⁰



Incorporation of halogen into a molecule is important because halides are often precursors for substitution or elimination reactions. The ability to convert alcohols to halides is therefore an important functional group transformation. The transform is

$$R \xrightarrow{R} Cl[Br, I] \longrightarrow R \xrightarrow{R} OH$$

2.9. ELIMINATION REACTIONS

There are several types of reactions in which a halogen, a sulfonate ester, or another functional group is lost from a molecule, along with hydrogen, or sometimes, functional group, to generate a carbon-carbon double bond. Alkenes and alkynes are formed by this process. This section will examine methods for the formation of such molecules via elimination reactions.²⁰¹ A monograph describes several different preparations of alkenes.²⁰²

2.9.A. Bimolecular 1,2-Elimination

Elimination is a major class of functional group exchange reactions in which a H atom and a leaving group are removed from a molecule, resulting in a π bond. However, removal of the hydrogen in this reaction relies on acid-base chemistry. Mechanistically, elimination is characterized by removal of a proton by a base, followed by expulsion of an atom or group (the leaving group, X) to form the π -bond in what appears to be a synchronous process. The reaction eliminates the elements of H and X, which leads to the name. We have discussed the characteristic features of nucleophiles and their reactions. In many cases, the nucleophile used in a substitution reaction is also a good Brønsted-Lowry base. Although there is strong attraction between the δ^+ dipole on the carbon bearing the leaving group and the base, collision with this carbon is unproductive in tertiary substrates due to the high energy of activation for the S_N2 transition state **69**. The bond polarization induced by the halide extends down the carbon

^{199.} Charpentier-Morize, M.; Sansoulet, J. Bull. Chim. Soc. Fr. 1977, 331.

^{200.} Baldwin, J.E.; Burrell, R.C. J. Org. Chem. 1999, 64, 3567.

^{201.} For examples see reference 3, pp 251-263, 569-580.

^{202.} Williams, J.M.J. (Ed.) Preparation of Alkenes, Oxford Press, Oxford, 1996.

chain to the β -hydrogen, which has a δ^+ dipole. Collision of the base with this β -hydrogen is an acid-base reaction that removes the hydrogen as indicated in **207**. As the base forms a bond to the β -H, negative charge develops on the β -carbon, and migration of the electron density toward the δ^+ dipole of the carbon bearing X generates a new π -bond (in alkene product **209**), with concomitant expulsion of the leaving group. This reaction follows second-order kinetics, and is given the designation of **E2 reaction** (bimolecular elimination). The E2 reaction is synchronous rather than stepwise,²⁰³ and all experimental observations can be explained by a transition state such as **208**. Note, however, that a "unified rule for elimination" has been proposed that predicts regioselectivity for a wide range of substrates.²⁰⁴ This rule appears to apply best when ion-pairing occurs, and is not as useful in cases where there is no ion paring.



The elimination sequence begins with an acid-base reaction, where the acid is a hydrogen atom attached to the β -carbon relative to the leaving group (the β -hydrogen, see **208**). Bond polarization resulting from the presence of electronegative nature of X makes that hydrogen δ^+ so it functions as a weak acid. It has been determined that as the added base reacts with the β -hydrogen, the favored rotamer for the molecule will have the leaving group and the β -hydrogen in an anti relationship (i.e. 180° apart).²⁰³ Electronic repulsion between the developing charge (electron pair) on the β -carbon and the leaving group is minimized in an anti- transition state. This requirement for an anti-relationship makes the stereochemistry of the alkene product predictable. In 208, the relative position of the alkyl groups in the anti transition state (note that R^1 and R^3 are on the same side) is retained in the alkene (209) as the π bond is formed. When halide **210A**, drawn as its Fischer projection, is treated with a base such as *tert*-butoxide, only the (Z)-alkene (211) is formed via E2 elimination. Halide 210A is the (2R,3S) diastereomer of 2-bromo-3-phenylbutane, and the rotamer that has the bromine leaving group and the β -hydrogen in an anti conformation is **210B**. The relative positions of phenyl and methyl are syn in **210B**, and after elimination of the elements of H (to *tert*-butoxide) and Br as the bromide ion (Z)-211 is formed. Similar reaction with the (2R.3R)-diastereomer of 2-bromo-3-phenyl-butane gives only (*E*)-2-phenyl-2-butene.

^{203. (}a) Saunders, Jr., W.H.; Cockerill, A.F. *Mechanisms of Elimination Reactions*, Wiley-Interscience, New York, *1973*; (b) Bordwell, F.G. *Acc. Chem. Res. 1972*, *5*, 374; (c) Dhar, M.L.; Hughes, E.D.; Ingold, C.K.; Masterman, S. J. Chem. Soc. *1948*, 2055, 2058, 2065; (d) Sneen, R.A. *Acc. Chem. Res. 1973*, *6*, 46, (e) Bordwell, F. G. *Ibid 1970*, *3*, 281.

^{204.} Gevorkyan, A.A.; Arakelyan, A.S.; Cockerill, A.F. Tetrahedron 1997, 53, 7947.



Using the **Hammond postulate** (a transition state will be structurally and energetically similar to the species nearest to it on the reaction path), the transition state for this reaction is product-like (a late transition state), so that factors stabilizing the alkene product will have a strong influence on the transition state. Alkyl groups that are attached to an sp² carbon release electrons to the π bond and enhance the strength of the π bond. A more highly substituted alkene is therefore more stable, and a relative order of alkene stability is:²⁰⁵

When there are two different β -hydrogen atoms, there is the possibility of forming two different alkene products (regioisomers). Removal of hydrogen in **212A** will lead to a double bond between C2-C3 [(*Z*)-3-ethyl-2-hexene], but removal of hydrogen from **212B** will lead to a double bond between C1-C2 (3-ethyl-1-hexene). These two alkenes are regioisomers. The transition state for **182A** leads to a more highly substituted alkene (3-ethyl-2-hexene) than does the transition state for **212B**, which leads to 3-ethyl-1-hexene. A trisubstituted alkene is thermodynamically more stable than a monosubstituted alkene. Since the Hammond postulate assumes a product-like transition state, **212A** leads to the more stable product and is favored over **212B**. Acid-base reactions are equilibrium processes and under thermodynamic control, so formation of the more stable product is favored. Formation of the more stable alkene for E2 reactions, and is usually termed **Saytzeff (Zaitsev) elimination**.²⁰⁶



The E2 transition state leads to strict conformational restraints with cyclic structures.²⁰⁷

To satisfy the anti-transition state for an E2 reaction in cyclohexane systems, reaction can

 ^{205. (}a) Brown, H.C.; Moritani, I. J. Am. Chem. Soc. 1953, 75, 4112, (b) Brown, H.C.; Moritani, I. Ibid 1956, 78, 2203; (c) Brown, H.C.; Nakagawa, M. Ibid 1956, 78, 2197.

^{206.} de la Mare, P.B.D. Progr. Stereochem. 1954, 1, 112.

^{207.} Reference 165, pp 189-194.

occur only if the β -hydrogen and the leaving group are trans-diaxial. Both equilibrating chair conformations **213A** and **213B** must be considered for elimination of bromine in trans-1-bromo-3-methylcyclohexane when a base is added, because two regioisomeric alkenes **214** and/or **215** are possible. Both alkenes have a disubstituted C=C unit and are approximately equal in stability. Based only on stability of products, we predict formation of both products in close to a 1:1 ratio.



Taking a closer look at this system, the bromine is equatorial in **213A**, and there are no β -hydrogens that can attain an anti conformation relative to the bromine. An E2 elimination cannot occur from **213A**. In **213B**, however, both H_a and H_b are anti to the axial bromine and elimination leads to **214** and **215**, respectively. Bromide **216** poses a different problem in that there are two β -hydrogens. There are two chair conformations (**216A** and **216B**), but **216B** is the thermodynamically more stable due to decreased *A* strain (sec. 1.5.D). In **216A** the two ethyl groups are axial and both β -hydrogens are equatorial and, therefore, not susceptible to base induced elimination is not possible. We therefore predict that treatment of **216** with base will *not* lead to an E2 reaction. The conformational characteristics of a cyclohexane, and possibly other ring systems, must be evaluated carefully because they may have a significant influence on reactivity in an E2 reaction.

MOLECULAR MODELING: Stereochemistry of Elimination of HX

Elimination of HX from a haloalkane or halocycloalkane typically follows an E2 mechanism that requires the leaving group to be *anti* to the β -hydrogen. The E2 reaction is an acid-base process in which the added base reacts with a slightly acidic proton on the carbon atom β to the leaving group, removing that proton. As the proton is removed, the developing charge migrates towards the α -carbon atom, leading to displacement of the leaving group and formation of a carbon-carbon double bond. Where there is more than one (different) β -hydrogen atom, the relatively acidity of the β -hydrogen atoms is an important issue in E2 reactions. As can be seen from the labeling experiment shown below, in the presence of base, 2-norbornyl chloride eliminates the *syn* hydrogen, which means that the dominant product results in elimination of DCl and not HCl. MOLECULAR MODELING: Stereochemistry of Elimination of HX, con't.



The accepted mechanistic explanation is that elimination probably involves initial deprotonation of 2-norbornyl chloride by alkoxide, followed by loss of chloride. In this case, the question is which "proton" (*syn* or *anti* to chlorine) is more susceptible to attack by alkoxide.

Examine a LUMO map for 2-norbornyl chloride. It is shown as a transparent model allowing you to see the underlying structure. Once you are oriented, you can switch to a solid model by *clicking* on the map and selecting *Solid* from the **Style** menu at the bottom of the screen. A LUMO map colors an electron density surface that gives the overall molecular size and shape (where a reagent can approach), with the (absolute) value of the lowest-unoccupied molecular orbital (LUMO). By convention, "blue" regions indicate large LUMO concentration and are likely to undergo attack by a nucleophile, while "red" regions indicate small LUMO concentrations. (Discussion of the use of LUMO maps to describe selectivity in nucleophilic additions to carbonyl compounds is provided in Chapter 4, section 4.7.B). Is the *exo* hydrogen (*syn* to Cl) more or less blue than the *endo* hydrogen (*anti* to Cl)? Which is more likely to be abstracted by the base? Is your result in agreement with what is actually observed? Is any other hydrogen "blue", that is, susceptible to nucleophilic attack? If so, which hydrogen and what is the product that should result? Is there any experimental evidence for this?

The leaving group in an E2 reaction can be a chloride, a bromide or an iodide, and also sulfonate esters such as a mesylate ($-OSO_2Me$), a tosylate ($-OSO_2p-Me-C_6H_4$), or a triflate ($-OSO_2CF_3$). The previously mentioned non-nucleophilic base DBN (**26**)^{208a} can be used to induce an E2 type reaction with primary halides. In a synthetic example taken from Alvarez-Manzaneda and co-worker's synthesis of (+)-austrodoral, DBU (**21**) reacted with acetate **217** to give conjugated ketone **218** in 95% yield.²⁰⁹ It does not remove H_b with elimination of acetate (an E2 process) nor H_c to generate the ester enolate (sec. 9.2). The nitrogen atom in the base DBN is sterically hindered, and a poor nucleophile. This means that the normal nucleophilic acyl addition to a carbonyl group in an ester or a ketone is very slow and not competitive with the elimination process. The two non-nucleophilic bases give moderate to good yields of alkene in E2 reactions with alkyl halides, and little or no substitution products. Even primary halides, which give mostly S_N2 reactions with nucleophilic bases, usually give an alkene in good yield. Non-conjugate alkenes can be formed, as in a study toward the synthesis of stenine by Padwa

For synthetic examples, see (a) Achab, S.; Das, B.C. J. Chem. Soc. Chem. Commun. 1983, 391; (b) Oediger, H.; Möller, Fr. Angew. Chem. Int. Ed. 1967, 6, 76.

Alvarez-Manzaneda, E.; Chahboun, R.; Barranco, I.; Cabrera, E.; Alvarez, E.; Lara, A.; Alvarez-Manzaneda, R.; Hmamouchi, M.; Es-Samti, H. *Tetrahedron* 2007, 63, 11943.

and $Ginn^{210}$ in which initial conversion of the alcohol unit in **219** to a mesylate followed by heating with DBU gave **220** in 64% overall yield.



The use of DBN and DBU in E2 reactions is somewhat selective, and the most common bases used are hydroxide (in water) or alkoxides in alcohol solvent (sodium methoxide in methanol, sodium ethoxide in ethanol, potassium *tert*-butoxide in *tert*-butanol).²⁰³ Amide bases such as sodium amide or lithium diethylamide can be used in ammonia or amine solvents. In these latter cases, the bases are also good nucleophiles, but in reactions with tertiary halides the elimination process dominates. With secondary halides, substitution can compete and with primary halides, S_N2 may be the major reaction, but this depends on the nature of the base/nucleophile. Apart from DBN and DBU, sterically hindered amines such as 2,2,6,6-tetramethylpiperidine have been used and the weaker base imidazole is important for elimination reactions with sensitive substrates. As with **219** \rightarrow **220**, sulfonate esters are good leaving groups commonly used in elimination reactions.

It is clear that a variety of substrates with different leaving groups can be converted to alkenes via elimination. β -Elimination of sulfones is also known.²¹¹ A general transform for the E2 reaction is



Note that vicinal dibromides can be treated with base in such a way that *both* bromine atoms are lost to generate an alkene. Many different reagents have been used for this transformation.²¹² Recently, indium metal was shown to be an effective reagent.²¹³

The E2 reaction can be applied to the synthesis of alkynes. When a vinyl halide is treated with a strong base, loss of HX by what is essentially an E2 process leads to formation of a triple

^{210.} Padwa, A.; Ginn, J.D. J. Org. Chem. 2005, 70, 5197.

^{211.} For a review of desulfonylation reactions see Nájera, C.; Yus, M. Tetrahedron 1999, 55, 10547.

^{212. (}a) Butcher, T.S.; Detty, M.R. J. Org. Chem., 1998, 63, 177; (b) Malanga, C.; Mannuccki, S.; Lardicci, L. *Tetrahedron* 1998, 54, 1021; (c) Khurana, J.M.; Maikap, G.C. J. O rg. Chem. 1991, 56, 2582; (d) Savoia, E.; Tagliavini, C.; Trombini, C.; Umani-Ronchi, A. J. Org. Chem. 1982, 47, 876; (e) Allred, E.L.; Beck, B.R.; Voorhees, K.J. J. Org. Chem. 1974, 39, 1426.

^{213.} Ranu, B.C. Eur. J. Org. Chem. 2000, 2347 (see pp 2348-2349).

bond. In a simple example, taken from Mori and co-worker's synthesis of the sphingosine derivative sulfobacin B,²¹⁴ 12-methyltridec-1-ene was treated with bromine in dichloromethane to give dibromide **221**. When this was treated with potassium *tert*-butoxide in petroleum ether, in the presence of 18-crown-6, initial elimination gave vinyl bromide **222**. Subsequent reaction with the base initiated an E2 reaction that gave alkyne **223** in 72% yield for both chemical steps. Note that this method of alkyne formation from vicinal bromides can lead to isomerization of the alkyne unit to give internal alkynes rather than terminal alkynes. Higher reaction temperatures and a large excess of base should be avoided.



An alternative method for preparing vinyl bromides can be incorporated into a synthesis of alkynes when combined with an olefination reaction (see sec. 8.8.A). In Ramachandran and co-worker's²¹⁵ synthesis of (–)-dictyostatin, aldehyde **224** was treated with carbon tetrabromide, triphenylphosphine and triethylamine to give vinyl dibromide **225** initially. Subsequent treatment with butyllithium led to elimination and an alkyne anion, and workup gave alkyne **226** in 83% yield. This sequence is commonly known as the **Corey-Fuchs procedure** (see chapter 8).²¹⁶ Note that this sequence is compatible with the presence of reactive functionality such as a tosylate leaving group. In Martin and co-workers' synthesis of (+)-8-*epi*-xanthatin,²¹⁷ aldehyde **227** was treated with carbon tetrabromide and triphenylphosphine to give vinyl dibromide (**228**).

Subsequent reaction with *n*-butyllithium and then triisopropylsilyl triflate (see chap. 7, sect. **7.3.A.ii**) gave the TIPS alkyne **229** in 70% overall yield. It is clear that extending the E2 reaction to prepare alkynes is quite useful as well as versatile.



^{214.} Takikawa, H.; Nozawa, D.; Kayo, A.; Muto, S.-e.; Mori, K. J. Chem. Soc. Perkin Trans. 1 1999, 2467.

^{215.} Ramachandran, P.V.; Srivastava, A.; Hazra, D. Org. Lett. 2007, 9, 157.

^{216.} Corey, E.J.; Fuchs, P.L. Tetrahedron Lett. 1972, 36, 3769.

^{217.} Kummer, D.A.; Brenneman, J.B.; Martin, S.F. Org. Lett 2005, 7, 4621.

The E2 disconnections to prepare alkynes are

$$R \xrightarrow{R} R \xrightarrow{R} R \xrightarrow{R} R \xrightarrow{X} Where X = halogen, OH, OR, OSO_2R R \xrightarrow{R} R \xrightarrow{R} R \xrightarrow{R} CHO$$

2.9.B. UNIMOLECULAR 1,2-ELIMINATION

The E2 reaction follows second-order kinetics, and the rate of reaction is proportional to the concentration of both the halide and the base. Under different reaction conditions, usually involving aqueous media, the reaction can follow first-order kinetics with an initial, slow ionization step to form a carbocation. In most cases (1) water is present, (2) a good leaving group is present, (3) a weak base is used, and (4) molecular rearrangements are often observed. As with the S_N1 reaction in sec 2.6.D, the rate of the reaction is given by the expression: Rate = k_1 [RX] + k_2 [nucleophile or base]. The slow, and rate determining step is ionization, followed by a fast removal of the β -hydrogen from the carbocation intermediate. Therefore, in this mechanism, there is no dependence on the concentration of the base and the observed overall rate is dependent only on the halide, leading to Rate = k [RX]. A simple example based on the generic mechanism of ionization to a carbocation and removal of a proton involves heating bromide 230 in aqueous media, in which the water assists in breaking the C-Br bond to generate a solvent separated ion pair (231). The resulting carbocation and bromide ions are solvated by water. The β -hydrogen of the carbocation (H_a in 231) is adjacent to a full positive charge, and polarized to a greater extent than the β -hydrogen in 230. Note that 231 may not be completely solvent separated, but we are assuming this is the case for simplicity. A base is required to remove H_a, but H_a in 231 is a stronger acid than H_a in 208 so a weaker base can be used for deprotonation. In this case, the water present in the reaction medium will suffice, and the electron pair from the C–H_a bond migrates toward the positive carbon to form a new π bond in the alkene product, 232. Rotation about the C-C bond in 231 prior to removal of H_a will lead to a mixture of rotamers, and 232 will be formed as a mixture of (E/Z)-isomers. The intermediacy of the planar carbocation allows facile attack at both faces of the carbocation, which leads to significant racemization at that carbon if the halide was enantiopure. In general, the thermodynamically more stable product will predominate (called Savtzeff elimination). The reaction is unimolecular in mechanism, and a nucleophile substitutes for the halide leaving group, so it is termed an E1 reaction (unimolecular elimination).^{218,219}

 ⁽a) Seib, R.C.; Shiner, Jr., V.J.; Sendijarevi'c, V.; Humski, K. J. Am. Chem. Soc. 1978, 100, 8133, (b) McLennon, D.J. Quart. Rev. Chem. Soc. 1967, 21, 490.

^{219.} Willstätter, R.; Waser, E. Berichte 1911, 44, 3423.



The S_N1 reaction usually competes with the E1 process in aqueous media since most bases used in this reaction are nucleophilic. Only when the gegenion is a very weak nucleophile will the E1 process dominate and produce substantial amounts of alkene product. Formation of an alkene when alcohols react with concentrated sulfuric acid or perchloric acid is an example, as when **233** was treated with concentrated sulfuric acid to give alkene **234**.²¹⁹ Non-oxidizing acids can be used, as in the treatment of **235** with *p*-toluenesulfonic acid in refluxing benzene to give an 86% yield of *E*-**236** in Shiina and co-worker's synthesis of tamoxifen.²²⁰ It is not always clear if the reaction proceeds by an E1 or an E2 mechanism since the oxonium ion derived from **235** can undergo an E2 reaction in the presence of sodium sulfate. Such mechanistic blurring is common, and often additives such as sodium sulfate are used to drive the reaction to the elimination product. If a carbocation intermediate is present, rearrangements are possible. Although sometimes useful, the E1 reaction is more commonly observed as a side reaction in S_N1 processes, or in E2 reactions in aqueous or alcohol media. If there is a mixture of E1 and E2 in a reaction, there is the possibility of E1 reactions when carbocation intermediates are generated in protic solvents.



2.9.C. Syn-Elimination Reactions

Both E2 and E1 reactions require a base and are intermolecular processes. For E2 reactions the hydrogen removed by the base must have an anti relationship to the leaving group. Another type of elimination process is possible if the basic atom is part of, or tethered to the substrate, but the β -hydrogen can only be removed if it eclipses the basic atom in a syn conformation.

^{220.} Shiinaa, I.; Sanoa, Y.; Nakata, K.; Suzuki, M.; Yokoyama, T.; Sasaki, A.; Orikasa, T.; Miyamoto, T.; Ikekita, M.; Nagahara, Y.; Hasome, Y. *Bioorganic & Med. Chem.* 2007, 15, 7599.

If the tethered base is also a leaving group, removal of the syn β -hydrogen is possible (an intramolecular process). This elimination process requires higher reaction temperatures since the requisite syn conformation is higher in energy (sec. 1.5.A). Such reactions are termed **syn elimination**.¹⁰⁴ There are several examples of this reaction involving different tethered bases that can also serve as leaving groups, and several are named reactions.

2.9.C.i. Hofmann Elimination. In a syn elimination, experimental results show that the less stable alkene is formed, and that the reaction is under kinetic control rather than thermodynamic control. The thermodynamically controlled E2 reactions require an anti-transition state. The kinetically controlled syn-elimination, however, requires a syn-transition state in which the β -hydrogen and the leaving group assume an eclipsed conformation. When there is more than one possibility, the lowest energy syn-eclipsed rotamer will be important for syn-eliminations. A classical example of this process is the **Hofmann elimination**, ^{108,104} illustrated by conversion of 2-bromo-3-methylbutane (237) to 3-methyl-1-butene (240). The bromide is first converted to ammonium bromide 238 by an $S_N 2$ reaction with trimethylamine. Ammonium salt 238 does not possess a basic atom or group (the bromide counterion is a weak basic). Bromide must be replaced with a stronger base, such as hydroxide before elimination can occur. Reaction with silver oxide (Ag₂O) in the presence of 1 equivalent of water (water cannot be the solvent or a co-solvent) gives the corresponding trimethylalkylammonium hydroxide (239). If water is present in excess, the ionic base would be solvent separated from the ionic ammonium moiety and an E2 reaction would result. In the absence of an ion separating solvent, however, the basic hydroxide is tethered to the ammonium ion by ionic bonding. Hydroxide can react with the β -hydrogen only when that C–H bond eclipses the C–NMe₃^{+ –}OH bond. When hydroxide reacts with this hydrogen, water is formed along with a π bond via expulsion of trimethylamine. In some cases, there is evidence that a nitrogen vlid intermediate is generated,²²¹ (sec. 8.8.C) but direct removal of hydrogen by hydroxide accounts for the product in most cases.²²²



It is possible to use the standard E2 model to evaluate the selectivity of the Hofmann elimination, when protic solvents such as water or ethanol are employed. In such a case, solvent separated ammonium and hydroxide ions are expected with an anti-transition state for removal of a β -hydrogen. First, note that in **239** there are two acidic β -hydrogens, H_a and H_b. The *anti-*

⁽a) Cope, A.C; Mehta, A.S. J. Am. Chem. Soc. 1963, 85, 1949, (b) Baldwin, M.A.; Banthorpe, D.V.; Loudon, A.G.; Waller, F.D. J. Chem. Soc. B, 1967, 509; (c) Ingold, C.K. Proc. Chem. Soc. 1962, 265; (d) Banthorpe, D.V.; Hughes, E.D.; Ingold, C.K. J. Chem. Soc. 1960, 4054.

^{222. (}a) Julian, P.L.; Meyer, E.W.; Printy, H.C. J. Am. Chem. Soc. 1948, 70, 887; (b) Banwell, M.G.; Austin, K.A.B.; Willis, A.C. Tetrahedron 2007, 63, 6388.

conformations for removal of H_a and also H_b in **239** are considered. The *anti*-conformation **241** leads to the less substituted alkene 3-methyl-1-butene (**240**) via removal of H_a . The *anti*-conformation **242** leads to the more substituted alkene 2-methyl-2-butene via removal of H_b . In **242** there is a *gauche*-interaction (see circled groups) that raises the energy of the resulting transition state relative to that from **241**, where this interaction is less. Conformation **241** is lower in energy and its transition state gives the major product, the less substituted alkene 1-pentene.



An alternative analysis of the Hofmann elimination will focus on a syn-conformation and intramolecular deprotonation via a N-ylid (see sec. 8.8.C). If the solvent is aprotic rather than or if there is no solvent at all (neat), one expects the ammonium hydroxide moiety will exist as a tight ion pair (no solvent separation). The only facile mechanism for removal of a β -hydrogen is, therefore, an intramolecular process that demands a syn-transition state. We return to 239 and the problem of two acidic β -hydrogens, H_a and H_b. Removal of either hydrogen via an intramolecular process requires a syn conformation, so 243 and 244 are the two important eclipsed conformations that must be considered. The methyl-methyl and methyl-hydrogen interactions in 244 (see \Leftarrow) are significantly higher in energy than the hydrogen-hydrogen and isopropyl-hydrogen interactions that arise in 243 (see sec. 1.5.A). Removal of H_a from the lower energy 243 will lead to the favored lower energy transition state and the observed major product 240. A synthetic transformation taken from Banwell and co-worker's synthesis of (+)-hirsutic acid uses the Hofmann elimination and also illustrates an alternative approach to this reaction. Reaction of iodomethane with the dimethylamine unit in 245 leads to the trimethylammonium salt. The usual Hofmann elimination sequence, with syn-elimination, gave the vinyl derivative, **246**.^{222b} This variation is important since using an amine as a Hofmann precursor is often more convenient than relying on an S_N2 reaction of an amine and a halide to produce the requisite ammonium salt (sec. 2.6.A).



Note that solvent effects are quite important in this reaction. A solvent that promotes complete solvent separation of the ammonium ion and the hydroxide ion will favor E2 and *anti*elimination, whereas a solvent that favors a tight ion pair will favor syn-elimination. In water, one anticipates extensive ion separation, but in ethanol or methanol, solvent separation is less efficient and the elimination may proceed by more than one mechanistic pathway.

Vital to the success of the Hofmann elimination is the use of an amine that does not possess β -hydrogens, such as trimethylamine or triphenylamine. Triethylamine has β -hydrogens on all three ethyl units and reaction with 3-iodo-2-methylpentane will give ammonium salt **247** where all four alkyl substituents attached to nitrogen have a β -hydrogen that can be removed by a base. Elimination via the most energetically favorable conformation will lead to the smallest and least substituted alkene, ethylene (from the ethyl units).^{221a,b} The other product is the tertiary amine, **248**. However, if one of the β -hydrogens is more acidic, such as that adjacent to the thiophene ring in **249**, Hofmann elimination leads to formation of a single alkene, **250**.²²³ This example also illustrates opening a bicyclic ring system to give a 10-membered ring, which is difficult to form using cyclization techniques (see sec. 6.6.B).



Syn-elimination can be extended to systems other than those required for Hofmann elimination, but a common feature is the presence of a basic atom connected to the molecule that is also a leaving group. The basic end of the molecule in the new system should be negatively charged or at least negatively polarized. As the dipole moment of the basic end of the molecule increases, the attraction for the δ^+ proton should increase, leading to greater facility of the syn elimination via transfer of hydrogen to the basic atom. Typically, this means that the reaction should occur at a lower reaction temperature. If the tethered base is a negatively charged ion, such as hydroxide in the Hofmann elimination, ion pairing with the cation is required if the synelimination is to occur and this places stringent solvent requirements on the system (see above). The leaving group ability of the base will influence the reaction temperature and facility of the syn elimination. For these new systems, the combination of a good base and a good leaving group in the molecule that is unstable to the reaction conditions as it departs, fragmentation to other products should drive the reaction to completion under milder conditions. A number of syn elimination reactions commonly used in synthesis exhibit the structural features just presented.

^{223.} Berkes, D.; Netchitaïlo, P.; Morel, J.; Decroix, B. Synth. Commun. 1998, 28, 949.

2.9.C.ii. Amine Oxide Pyrolysis (Cope Elimination). Using the Hofmann elimination as a prototype, modification of the leaving group can facilitate syn-elimination. Specifically, the hydroxide ion (the base) and ammonium ion (the leaving group) pair can be replaced with a basic atom or group that is part of the leaving group. Cope found that incorporation of an amine *N*-oxide (R_3N-O) satisfied this new criterion (see 251). The negative oxygen dipole of an amine oxide function as a base, and removal of the β -hydrogen via a syn conformation leads to cleavage of the C–N bond and loss of the resulting neutral leaving group, N.N-dimethylhydroxylamine. The base is part of the molecule and not a separate molecule, and the E2 elimination is not competitive. Such reactions generally require higher reaction temperatures relative to an E2 process. Heating amine oxides to produce alkenes is known as **Cope elimination**,^{224,108d,104} and a typical reaction temperature is 120°C, significantly lower than that required for the Hofmann elimination as shown for the conversion of 251 to 252.^{108d} A Cope elimination requires the synthesis of N-oxides, and these are usually formed by oxidation of the corresponding amine with hydrogen peroxide or *m*-chloroperoxybenzoic acid²²⁵ (sec. 3.9.B). The reaction is not limited to dimethylamines, although the temperatures required for elimination will vary with the structure of the amine oxide. In a synthesis of (-)-cuparene,²²⁶ Grainger and Patel oxidized amine 253 to N-oxide 254 in 83% yield with m-chloroperoxybenzoic acid. Subsequent heating to 200°C in DMSO, in the presence of microwave irradiation for one minute, gave a 72% yield of 255. In the absence of microwave irradiation, heating 254 to 60°C in THF for 8 hours gave a 40% yield of 255. Note that alkenyl-*N*-methylhydroxylamines can undergo a reverse Cope elimination to give pyrrolidine- or piperidine N-oxides.²²⁷



^{224. (}a) Cope, A.C.; Foster, T.T.; Towle, P.H. J. Am. Chem. Soc. 1949, 71, 3929; (b) Cope, A.C.; Pike, R.A.; Spencer, C.F. Ibid 1953, 75, 3212; (c) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-19.

- 226. Grainger, R.S.; Patel, A. Chem. Commun. 2003, 1072.
- 227. Ciganek, E.; Read, Jr., J.M.; Calabrese, J.C. J. Org. Chem. 1995, 60, 5795.

^{225. (}a) Cope, A.C.; Ciganek, E. Org. Syn. Coll. Vol. 4 1963, 612, (b) Craig, J.C.; Purushothaman, K.K. J. Org. Chem.1970, 35, 1721.

2.9.C.iii. Ester Pyrolysis.^{228,104} Other functional groups can be incorporated into a molecule that will facilitate syn-elimination via intramolecular removal of a β -hydrogen. A simple example is an acetoxy group (–OCOMe), where the carbonyl oxygen of the ester functions as a tethered base. Clearly, this oxygen is a weak base and acetic acid from acetate is a poorer leaving group relative to an amine from an ammonium salt or a *N*,*N*-dialkylhydroxylamine from an amine oxide. Indeed, syn elimination of acetates (with loss of acetic acid) requires higher reaction temperatures. On the other hand, acetates are readily available by reaction of an alcohol with acetic anhydride or acetyl chloride and pyridine (or another base). For **256**, heating to 450°C was required for elimination to the alkene product (**257**) and in this example the deuterium was retained.^{228b,229} Similar pyrolysis of the enantiomer (**258**) gave alkene **259** in which the deuterium from the β -carbon by the acetoxy group from the lowest energy syn-rotamer.^{228c,104}



The importance of the syn relationship of a β -hydrogen and the leaving group is seen in hydrindanes **260** and **261**, which both produced **262** upon pyrolysis. The syn-derivative (**260**) required temperatures at least 200°C higher than the anti-acetate (**261**).^{228b} Asynthetic example taken from Basabe and co-worker's synthesis of (+)-lagerstronolide from (+)-sclareol,²³⁰ illustrates two key points with this reaction. When diacetate **264** was heated on silica gel (a variation of the basic reaction), a mixture of three alkenes were formed in 90% yield, which were difficult to separate and used in subsequent reactions as a mixture. It is likely that **264** was the favored product and isomerized under the reaction conditions. Note that such isomerization of the exo-methylene group is common with heating. Note also that the acetate unit at the tertiary carbon eliminated in preference to the acetate at the secondary carbon, which is also typical in this type of syn elimination.



 ⁽a) Alexander, E.R.; Mudrak, A. J. Am. Chem. Soc. 1950, 72, 1810; (b) Idem Ibid 1950, 72, 3194; (c) Curtin, C.Y.; Kellom, D.B. Ibid 1953, 75, 6011.

^{229.} Jung, M.E.; Lyster, M.A. J. Org. Chem. 1977, 42, 3761.

^{230.} Basabe, P.; Bodero, O.; Marcos, I.S.; Diez, D.; de Román, M.; Blanco, A.; Urones, J.G. *Tetrahedron* 2007, 63, 11838.



2.9.C.iv. Xanthate Ester Pvrolvsis.^{231,104,228a,b} The high temperatures required for acetate pyrolysis greatly limits the synthetic utility of this reaction. Improved leaving group ability and a greater basicity of the tethered base would improve the reaction if departure of the leaving group generated a product that was more stable or if that product decomposed after its departure. In either case the elimination would be more facile. The sulfur analog of a carbonate is called a xanthate, O(C=S)-SR, and satisfies the goals for improved syn-elimination. The xanthatae group is a better leaving group than acetate, but sulfur is a poorer base than oxygen, although it is a better nucleophile.^{232,93,101,102} Elimination occurred at significantly lower temperatures relative to an acetate ($\sim 200^{\circ}$ C), and the neutral molecule 268 was lost as a byproduct. This product fragmented to COS and methanethiol, making the elimination essentially irreversible. In a specific example, the thiocarbonyl group of xanthate 265 fragmented to 266 and 267, with the less substituted **266** being the major isomer. This reaction is one step of the **Chugaev** elimination^{233,231} used for conversion of alcohols to alkenes.²³¹ The xanthate ester was prepared from the corresponding alcohol by reaction with carbon disulfide to give a thioanion $(R-OCS_{2})$, followed by reaction with iodomethane to give 265. A synthetic example is taken from a synthesis of (-)-kainic acid by Ogasawara and co-workers,²³⁴ in which alcohol 269 was converted to xanthate ester 270 in 92% yield. Subsequent heating in refluxing diphenyl ether gave 271, but under these conditions an ene reaction (sec. 11.13) led to formation of **272** in 72% yield. Since we have not yet discussed the ene reaction, the key carbon atoms are numbered in 271 and 272 so that one can follow the transformation.



234. Nakagawa, H.; Sugahara, T.; Ogasawara, K. Org. Lett. 2000, 2, 3181.

^{231.} Nace, H.R. Org. React. 1962, 12, 57.

^{232. (}a) Wells, P.R. Chem. Rev. 1963, 63, 171, (b) Koskikallio, J. Acta Chem. Scand. 1969, 23, 1477, 1490.

⁽a) Tschugaeff, L. *Berichte* 1899, 32, 3332; (b) DePuy, C.H.; King, R.W. *Chem. Rev.* 1960, 60, 441 (see p 444); (c) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-17.



There are alternative elimination pathways for xanthate esters. Epoxy-alcohol **273** was converted to xanthate ester **274** in quantitative yield using standard conditions. The elimination step used triethylsilane (Et₃SiH), a radical initiator such as AIBN, and treatment with tetrabutylammonium fluoride (TBAF). Under these conditions, opening of the epoxide ring was accompanied by elimination to give **275** in 72% yield in Ogasawara and co-worker's synthesis of (+)-frontalin.²³⁵ This elimination is related to the **Barton-McCombie reaction** involving reduction of xanthates under radical conditions (see sec. 4.9.H).



2.9.C.v. Sulfoxide Pyrolysis.²³⁶ A very useful change in the syn elimination precursor incorporates the polarized oxygen of a sulfoxide. If a sulfide is oxidized with peroxide or with sodium *meta*-periodate (NaIO₄),²³⁷ the resulting sulfoxide has a highly polarized S–O bond (sec. 3.9.A). The negatively polarized oxygen of sulfoxides (*S*-oxides) can function as a tethered base with the O–S–R moiety serving as a leaving group. If the β-hydrogen and the S–O moiety assume an eclipsed conformation, the basic oxygen removes the hydrogen to generate PhS–OH (benzenesulfenic acid where sulfur is bonded to a phenyl group). This product is unstable to the reaction conditions and decomposes, facilitating the elimination. An example

^{235.} Kanada, R.M.; Tankguchi, T.; Ogawawara, K. Tetrahedron Lett. 2000, 41, 3631.

^{236. (}a) Grieco, P.A.; Reap, J.J. Tetrahedron Lett. 1974, 1097; (b) Montanari, F. Int. J. Sulfur Chem. C, 1971, 6, 137 [Chem. Abstr. 76:24243b 1972]; (c) Trost, B.M.; Salzmann, T.N. J. Org. Chem. 1975, 40, 148; (d) Kingsbury, C.A.; Cram, D.J. J. Am. Chem. Soc. 1960, 82, 1810.

^{237. (}a) Grieco, P.A.; Miyashita, M. J. Org. Chem. 1974, 39, 120; (b) Mitchell, R.H. J. Chem. Soc. Chem. Commun. 1974, 990; (c) Sharpless, K.B.; Young, M.W.; Lauer, R.L. J. Am. Chem. Soc. 1973, 95, 2697; (d) Sharpless, K.B.; Young, M.W.; Lauer, R.L. Tetrahedron Lett. 1973, 1979; (e) Jones, D.N.; Mundy, D.; Whitehouse, R.D. J. Chem. Soc. Chem. Commun. 1970, 86; (f) Reich, H.J.; Renga, J.M.; Reich, I.L. J. Org. Chem. 1974, 39, 2133, (g) Sharpless, K.B.; Young, M.W. Ibid 1975, 40, 947.

is taken from a synthesis of precursors of the agalacto (exo) fragment of the quartromicins by Roush and Qi,²³⁸ in which the sulfide unit in **276** was oxidized to the corresponding sulfoxide (**276**) with *m*-chloroperoxybenzoic acid (sect. 3.9.A.i). Subsequent heating in toluene gave **278** in good yield.



In addition to phenyl sulfoxides, methyl sulfoxides (-S(O)Me) can also be prepared, and they undergo syn-elimination when heated, but the temperature required for pyrolysis is $\approx 150^{\circ}C$. When R is phenyl, elimination can often be observed by heating to only 80°C, although toluene at 100°C was used for 277.

2.9.C.vi. Selenoxide Pyrolysis.²³⁸ Just as sulfides are oxidized to sulfoxides, selenides (R-Se-R) can be oxidized to selenoxides. Analogous to a sulfoxide, heating a selenoxide leads to thermal syn-elimination to give the less substituted alkene. The increased polarity of the Se-O bond of the selenoxide, relative to the S-O bond of the sulfoxide, and the loss of the unstable R-Se-OH leads to even lower temperatures for thermal syn-elimination (typically 0-25°C). Elimination of PhSeOH from **279** gave the exocyclic-methylene derivative (**280**) as the major product, rather than the endocyclic alkene.^{250a} This elimination occurred at 0°C, and selenoxide elimination is a particularly attractive method for the generation of sensitive alkenes such as the less stable exocyclic methylene lactone (**280**). In this particular case, the steric constraints for isomerization found in the bicyclic selenoxide **280** are also important. Note that *selenium compounds are toxic* and great care should be exercised in the handling and disposal of all materials.



There are many synthetic examples that use this technique. In a synthesis of (–)-aristolochene by Pedro and co-workers,²³⁹ selenide **281** was treated with aqueous hydrogen peroxide at 0°C to give the selenoxide. Simply warming to ambient temperature induced elimination to give alkene **282** in 69% yield, despite the presence the sensitive epoxide functional group.

^{238.} Qi, J.; Roush, W.R. Org. Lett. 2006, 8, 2795.

^{239.} Blay, G.; Cardona, L.; Collado, A.M.; Garcia, B.; Pedro, J.R. J. Org. Chem. 2006, 71, 4929.



Selenides can undergo another type of elimination reaction, when the selenium unit is attached to a carbon adjacent to a thiocarbamate group as in **281**. Radical induced elimination with AIBN in the presence of a hydrogen atom donating species such as tributyltin hydride (see sec. 13.3) gave the elimination product **282** in 82% yield, which was used in Comins and Kuethe' synthesis of (+)-cannabisativine.²⁴⁰ Note that **281** was generated *in situ* from an alcohol precursor and the thiocarbamate formation-elimination steps were done in a one-pot reaction.

Factors other than bond polarization and leaving group ability influence the ease of thermolysis, illustrated by xanthate ester pyrolysis. DePuy and King state "the much greater ease of xanthate pyrolysis as compared to the pyrolysis of esters must be due to an added driving force as a consequence of conversion, in the transition state, of the system -O-CS into the system O=C-S-. Examination of the relative bond energies shows that conversion should be exothermic to the extent of nearly 20 kcal mol⁻¹ (83.7 kJ mol⁻¹)".¹⁰⁴ Bond polarization is, however, a convenient handle for predicting the relative ease of syn elimination in many cases, although it accounts for only part of the difference in actual reactivity and product formation. It is also known that *n*-alkyl aryl selenides that have an ortho-substituent on the aromatic ring are superior reagents for oxidation and syn-elimination when compared to those compounds having a para-substituent.²⁴¹ Structural effects therefore play a role in the reaction.

The retrosynthetic transform for syn elimination is that shown for the anti elimination reactions except that the less substituted alkene is the target:



2.9.C.vii. Burgess Reagent.²⁴² Another reagent, (carboxysulfamoy1)triethylammonium hydroxide inner salt methyl ester (283, the Burgess reagent) follows a syn-elimination mechanism, and is quite useful for introducing an alkene unit into a substrate. Reaction of

^{240.} Kuethe, J.T.; Comins, D.L. Org. Lett. 2000, 2, 855.

^{241.} Sayama, S.; Onami, T. Tetrahedron Lett. 2000, 41, 5557.

^{242. (}a) Burgess, E.M.; Penton Jr., H.R.; Taylor, E.A. J. Org. Chem. 1973, 38, 26; (b) Atkins Jr., G.M.; Burgess, E.M. J. Am. Chem. Soc. 1968, 90, 4744; (c) Crabbé, P.; León, C. J. Org. Chem. 1970, 35, 2594. For a chiral Burgess reagent, see (d) Leisch, H.; Saxon, R.; Sullivan, B.; Hudlicky, T. Synlett 2006, 445; (e) Sullivan, B.; Gilmet, J.; Leisch, H.; Hudlicky, T. J. Nat. Prod. 2008, 71, 346.

an alcohol with **283** leads to **284**, and heating initiates the elimination to give the alkene. The Burgess reagent does not appear to be as selective for syn elimination as the preceding reagents. In general, as stated directly by Burgess, there is a cis stereochemical constraint and Saytzeff elimination is observed in aliphatic cases.²⁴² When **283** was heated with **285** in acetonitrile, for example, a 1:1 mixture of the exocyclic alkene (**286**) and endocyclic alkene (**287**) was formed in 80% yield.²⁴² Rearrangement is observed in some cases. Nonetheless, the Burgess reagent can be quite valuable in fine organic synthesis. In a synthesis of momilactone A by Deslongchamps and Germain,²⁴³ alcohol **288** was heated with **283** in refluxing toluene, to give a 40-50% yield of momilactone A (**289**).



2.9.D. 1,3-Elimination (Decarboxylation)

Sections 2.9.A-C focused on 1,2-elimination reactions. The syn elimination reactions just discussed showed that intramolecular removal of an acidic hydrogen leads to loss of a leaving group and formation of a π -bond. Elimination can also occur when an acidic hydrogen and a leaving group are separated by three atoms, in what is termed 1,3-elimination. When a carboxyl carbon is β to a π -bond (a carbonyl, alkene or aryl) the acidic hydrogen of the acid can be transferred to the oxygen of the carbonyl (or to the sp² carbon of alkenes or aryls) via a sixcenter transition state. This requires a syn-orientation of the carbonyl oxygen and the carboxyl hydrogen, as was observed in syn 1,2-elimination. This thermal process results in cleavage of the bond connecting the carboxyl carbon, loss of carbon dioxide and formation of a new π bond. This 1,3-elimination process is called **decarboxylation** and is a common reaction of β -keto-acids, β -carboxyl esters, and 1,3-diacids (malonic acid derivatives). A simple example

^{243.} Germain, J.; Deslongchamps, P. J. Org. Chem. 2002, 67, 5269.

is the elimination of carbon dioxide from 3-oxopentanoic acid (**290**) to give an enol, which tautomerizes to 2-butanone. Structure **290** is drawn in a way that emphasizes the transfer of hydrogen to the oxygen of the ketone moiety occurs via a six-center transition state. The **malonic acid synthesis** (sec. 9.3.A) generates substituted malonic esters that can be saponified to diacids such as **292**. In one example, treatment of diethyl malonate with sodium ethoxide and then 6-bromo-(2*E*)-hexene gave a 72% yield of **291**.²⁴⁴ Saponification with aqueous KOH gave a 99% yield of **292**, which upon heating to 160°C for 5 h gave a 94% yield of **294**, in Clive and Hisaindee's synthesis of brevioxime.²⁴⁴ The initially formed product of decarboxylation is an enol (in this case **293**) and this enol form of the acid tautomerized to the isolated product, **294**. Decarboxylation begins with an internal acid-base reaction, where the acid is the O–H unit of the carboxylic acid, and the base is the oxygen of the carbonyl β to the acid moiety. Decarboxylation is assisted by loss of a neutral leaving group carbon dioxide.



Krapcho and co-workers developed a mild decarboxylation procedure of esters.²⁴⁵ In a synthesis of deacetoxyalcyonin acetate by Molander and co-workers,²⁴⁶ β -keto methyl ester **295** (drawn in its enol form) was heated with LiCl in aqueous DMSO to give decarboxylation and a good yield of **296**. This mild procedure is referred to as **Krapcho decarboxylation**.²⁴⁷ An alternative procedure has been reported. In a synthesis of (–)-gilbertine by Blechert and Jiricek,²⁴⁸ heating **297** with DABCO, in toluene and water, gave **298** in 66% yield.

^{244.} Clive, D.J.; Hisaindee, S. J. Org. Chem. 2000, 65, 4923.

^{245. (}a) Krapcho, A.P.; Weimaster, J.F.; Eldridge, J.M.; Jahngen, Jr., E.G.E.; Lovey, A.J.; Stephens, W.P. J. Org. Chem. 1978, 43, 138; (b) Krapcho, A.P. Synthesis 1982, 805, 893.

^{246.} Molander, G.A.; St. Jean, Jr., D.J.; Haas, J. J. Am. Chem. Soc. 2004, 126, 1642.

^{247. (}a) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-53; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 380-381.

^{248.} Jiricek, J.; Blechert, S. J. Am. Chem. Soc. 2004, 126, 3534.



Decarboxylation is also observed with conjugated carboxylic acids such as **299**. In conjugated acids, the C=C unit attacks the acidic proton of the COOH unit via a six-centered transition state leading to decarboxylation. The alkene unit can be even further removed from the acid, as in Smith and co-worker's synthesis of zampanolide²⁴⁹ in which **299** was heated to 130°C in quinoline for 3 hours. The proximal C=C unit functioned as the internal base, and decarboxylation led to a 79% yield of **300**. In general, the π bond of an alkene is a much weaker base than the oxygen of a carbonyl so the hydrogen transfer is less efficient. This fact usually means that higher reaction temperatures are required for the decarboxylation, and additives such as quinoline are often required.



Decarboxylation of conjugated acids proceeds with bond migration, as shown in the transformation of $299 \rightarrow 300$. Such bond migration must be accounted for in any synthetic plan. Another source of π bonds are aromatic rings. Transfer of the acidic hydrogen of the acid to the π -bond of an aryl carbon is more difficult than with simple alkenes. First, the π bond is a weaker base due to resonance delocalization and second, accepting the hydrogen requires that the aromatic nature of the benzene ring be disrupted. For both reasons higher energy is required for the reaction, which means higher reaction temperatures for thermolysis of 301 relative to benzylic systems such as 303. The decarboxylation proceeds by the usual sixcenter transition state to give benzylidene intermediate 302, which is unstable to the thermal conditions of the reaction and quickly aromatizes to 303.

^{249.} Smith III, A.B.; Safonov, I.G.; Corbett, R.M. J. Am. Chem. Soc. 2002, 124 11102.



2.9.E. 1,3-Elimination (Grob Fragmentation)

Both 1,2-elimination reactions and decarboxylation reactions require attack at an acidic hydrogen, which is accompanied by concomitant bond cleavage that releases a leaving group and forms a π bond. Other types of elimination reactions are possible if the electron-donating species and the leaving group are properly positioned. If the basic atom and the leaving group are separated by at least three carbons and the bonds that are made and broken assume an anti relationship, elimination is possible. Prelog first observed this reaction in work that solved the structure of quinine and other Cinchona alkaloids. This work involved degradation studies that included treatment of **304** with KOH and silver nitrate. Silver ion reacted with the bromide to give a carbocation (**305**).



Subsequently, the nitrogen lone pair induced a 1,3-elimination ring-opening reaction, as shown, to give iminium salt **306**.²⁵⁰ In the presence of aqueous hydroxide in the reaction medium, addition to the iminium salt led to loss of formaldehyde and formation of the final product, **307**. Transfer of the nitrogen lone electron pair toward the leaving group (or the carbocation center) required the N–C bond and the C–C⁺ bond to have an anti relationship. This anti relationship is taken from Prelog's proposed synchronous mechanism for the 1,3-elimination, and can be generalized to say that "both the C_{α} –X bond and the orbital of the nitrogen lone pair be antiperiplanar to the C_{β} -C_{γ} bond".^{251,252} Grob, et al. later expanded this 1,3-elimination to include amino halides and amino sulfonates.²⁵³ The synchronous nature of the reaction was confirmed by Grob and is illustrated by the elimination of the tosylate group in **308** and **310**.²⁵² Elimination of the 5 β -isomer (**308**) gave the (*E*)-isomer (**309**), whereas elimination of

^{250. (}a) Prelog, V.; Zalán, E. Helv. Chim. Acta 1944, 27, 535; (b) Prelog, V.; Häfliger, O. Ibid 1950, 33, 2021.

^{251.} Klyne, W.; Prelog, V. Experientia 1960, 16, 521.

^{252.} Grob, C.A. Angew. Chem. Int. Ed. 1969, 8, 535 and references cited therein.

^{253.} Grob, C.A.; Kiefer, H.R.; Lutz, H.J.; Wilkens, H.J. Helv. Chim. Acta 1967, 50, 416.

the 5 α -isomer gave the (Z)-isomer (**311**), along with **311**. The stereochemistry of the products is best explained if the pertinent orbitals are antiparallel in the transition state leading to the elimination. The reaction rates for both of these substrates were rather high, but the 5 α -isomer (**310**) reacted much slower and gave a mixture of the substitution product (**311**) in addition to the elimination product (**312**). This latter result led to a more general conclusion that the usual S_N2 reaction expected with a tosylate and a nucleophile such as hydroxide will occur unless the rate of the synchronous elimination is fast. Although the reaction was discovered by Prelog, Grob's contributions to this reaction led to its bearing his name, the **Grob fragmentation**.²⁵⁴



Both ionization and elimination processes are possible in these systems, as illustrated by generic structure **313**. Compound **313** gives the elimination products (iminium ion **314** and the alkene) with a rate constant k_f and the ionization product **315** with a rate of k_i . This latter pathway leads to substitution. The synchronous fragmentation can occur only if the k_f is comparable with or greater than the rate of ionization k_i for the γ -amino carbon ($k_f \ge k_i$).²⁵³ If the stereochemical requirements are satisfied, k_f is the dominant term. This increase in reactivity due to synchronous fragmentation is referred to as the **frangomeric effect**, and expressed by $f = k_f/k_i$. This effect is not limited to amines or carbocations derived from alkyl halides and silver salts. Suitable derivatives of 1,3-diols also undergo this fragmentation.²⁵⁵ A synthetic example is taken from Paquette and co-worker's synthesis of jatrophatrione,²⁵⁶ in which mesyl-alcohol **316** was treated with potassium *tert*-butoxide, and fragmentation gave alkoxide **317** (hydrogen atoms removed in the 3D model for clarity). As shown, the mesylate leaving group is properly oriented relative to the alkoxide for a Grob fragmentation leading to **318**, in 98% yield.



^{254. (}a) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-39; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 288-289.

^{255.} Zimmerman, H.E.; English, Jr., J. J. Am. Chem. Soc. 1954, 76, 2285, 2291, 2294.

^{256.} Paquette, L.A.; Yang, J.; Long, Y.O. J. Am. Chem. Soc. 2002, 124, 6542.



The alkoxide required to initiate a Grob fragmentation can be generated in several ways. Direct reaction of an alcohol with a suitable base to form the alkoxide is one way, as seen in **317**. An alternative route is carbanion addition to a carbonyl followed by a Grob fragmentation, as was used in Magnus and Buddhsukh's synthesis of hinesol.²⁵⁷ Another example is taken from Baran and co-workers synthesis of vinigrol in which **319** was treated with potassium hexamethyldisilazide to give alkoxide **320**. The mesylate leving group is posiinted to allow the Grob fragmention, whechn gave **321** in 93% yield²⁵⁸ A radical-induced Grob-type fragmentation has also been reported in a synthesis of terpenoids.²⁵⁹



2.9.F. Other 1,3-Elimination Reactions

A number of 1,3-elimination processes other than those described above have been observed. A brief introduction of a few typical reactions will suffice. Treatment of diketone **322** with hydroxide initially gave the expected addition product **323**, but ring opening generated an enolate anion (**324**). Formation of the resonance stabilized enolate anion (sec. 9.2) was the driving force of this fragmentation. Internal proton transfer gave **325**, and hydrolysis led to the observed product, keto-acid **326**.²⁶⁰



^{257. (}a) Buddhsukh, D.; Magnus, P. J. Chem. Soc. Chem. Commun. 1975, 952; (b) Chass, D.A.; Buddhsukh, D.; Magnus, P.D. J. Org. Chem. 1978, 43, 1750.

^{258.} Maimone, T.J.; Voica, A.-F.; Baran, P.S. Angew. Chemie. Int. Ed. 2008, 47, 3054.

^{259.} Lange, G.L.; Gottardo, C.; Merica, A. J. Org. Chem. 1999, 64, 6738.

^{260.} Stetter, H. Angew. Chem. 1955, 67, 769.



Elimination of carbon dioxide (CO₂) has been observed from β -halo carboxylates. When β -bromo acrylic acid **327** was treated with aqueous hydroxide, for example, 1,3-elimination of bromide from the carboxylate anion **328** gave alkene **329** along with carbon dioxide.²⁶¹ In some cases, homoallylic alcohols can eliminate an aldehyde moiety. An example is the pyrolysis of **330** at 500°C to give methylenecyclohexane (**331**) along with the aldehyde heptanal (**332**). This fragmentation occurs via a six-center transition state,²⁶² although it could be also be described as a *retro*-ene reaction (see sec. 11.13).



This section has described several synthetically important 1,2- and 1,3-elimination processes. In both cases substitution can be a competitive reaction, but proper choice of reaction conditions will maximize formation of the elimination products. Several interesting disconnections that are possible with substrates capable of undergoing 1,2- and 1,3-eliminations are shown.

$$R \xrightarrow{O}_{CO_{2}H} R \xrightarrow{O}_{R^{2}} R \xrightarrow{O}_{R^{2}} R \xrightarrow{R}_{R^{2}} R \xrightarrow{CO_{2}H}_{CO_{2}H} R \xrightarrow{O}_{CO_{2}H} R \xrightarrow{$$

2.10. ADDITION REACTIONS

Acids and bases have figured prominently in all of the reactions described in this chapter. We have previously explored the concept that an alkene can function as a base. In this section, the π bond of an alkene or an alkyne will be used as a base with protonic acids, Lewis acids, and with other electrophilic atoms. When an alkene donates an electron pair (acts as a base) to a proton, the π bond breaks and forms a new C–H bond to one carbon of the old C=C unit. The

^{261. (}a) Grovenstein, Jr., E.; Lee, D.E. J. Am. Chem. Soc. 1953, 75, 2639; (b) Cristol, S.J.; Norris, W.P. Ibid 1953 75, 2645.

^{262.} Arnold, R.T.; Smolinsky, G. J. Am. Chem. Soc. 1959, 81, 6443.

other carbon of the C=C unit becomes a carbocation, and is subject to subsequent substitution or elimination reactions. If the alkene donates the electrons to a Lewis acid, the resulting complex will lead to other products. Recognizing the basicity of alkenes and alkynes will help explain the reactions discussed in this section.

The elimination reactions presented in Sec. 2.9 are important in synthesis, and usually involve conversion of an alcohol or alkyl halide to an alkene or alkyne. Many functional group interchange reactions involve interconversion functional groups, as in the conversion of an alkene or alkyne to an alkyl halide or an alkyl halide to an alkene or alkyne. The reaction in which a new atom or group is transferred to each carbon of the π bond forms two new sp³ bonds as the π bond is broken, and the overall process is called an **addition reaction** since the atoms re "added" to the π -bond.²⁶³ A general reaction for addition of a reagent to an alkene is the conversion of **333** to **334**. This addition process encompasses many reaction types, but for synthetic planning, it is convenient to classify addition reactions into four mechanistic categories. (1) Those involving free and metal stabilized ions as intermediates. (2) Those involving symmetrically bridged ions as intermediates. (3) Addition via a four-center transition state. (4) Nucleophilic acyl addition, discussed previously in sec. 2.5.



Nucleophilic acyl addition was discussed in sec. 2.5. The main examples of four-center transition state additions are hydroboration, which will be discussed in chapter 5, and hydride reduction of carbonyls, which will be discussed in section 4.2-4.5. This section will therefore focus on categories 1 and 2.

2.10.A. π -Bonds as Brønsted-Lowry Bases

The π -bond of an alkene can react as a Brønsted-Lowry base in the presence of a protonic acid such as HCl or HBr, where an electron pair is donated to the acid (H⁺) to form a new C–H bond. The reaction only occurs with relatively strong mineral acids, so the alkene is considered to be a weak base. In a reaction with HBr and cyclohexene, the π -bond is broken as the new Br–C bond is formed and a carbocation is generated on the adjacent carbon atom of the C=C unit. The reaction of cyclohexene with HBr therefore generates secondary cation **335**. The cationic center in **335** is subsequently attacked by the nucleophilic gegenion (Br⁻ from HBr) to produce bromocyclohexane. The latter portion of this sequence is analogous to the second step (coupling) of an S_N1 reaction. It is usually assumed that the initial reaction will form of a solvent separated carbocation intermediate, but this depends on the solvent. A tight ion pair intermediate can react in the substitution step to give the same product. The net result of this

^{263.} For examples see reference 3, pp 629-666, 912-915.

cationic reaction is *addition* of H and Br across the π bond. The carbocation center is planar, allowing the nucleophilic bromide to approach from either face, so the addition reaction give a racemic product.



Alkenes are rather weak bases and will react only with strong acids. This limits the reaction to strong acids HX (such as HCl, HBr, H_2SO_4 , HNO₃, etc.), which react with alkenes to form an alkyl halide, sulfate, nitrate, and so on. Alkyl sulfates and nitrates are often unstable, and undergo elimination reactions or decompose. In many cases, this instability (including elimination and ionization) means those products cannot be formed at all. When HClO₂ or HBF₄ are used, ClO_4^- and BF₄⁻ are very weak nucleophiles and react slowly with the cation intermediate. In such a case, another nucleophile can be added that will react preferentially with the cation. If water is present (it may come from an aqueous solvent), reaction with the carbocation intermediate will give an alcohol product. If a more nucleophilic reagent such as KCN is added to the reaction, a nitrile can be formed. From a synthetic viewpoint, this option greatly expands the utility of the reaction, allowing introduction of a nucleophilic unit (Y) that is not a part of the initial acid (HX). Since a carbocation is formed during the addition process, it is subject to the rearrangement problems inherent to such species (sec. 2.6.B.iii). This process is under thermodynamic control and tends to give the more stable ion, and the more stable final product. Before the mechanistic nature of this reaction was understood it was observed that reactions of alkenes and acids always produced the more substituted product, which is the so-called Markovnikov addition,^{264,265} of simple alkenes. In other words, addition of HCl, HBr, or HI to substituted alkenes will lead to an alkyl halide where the nucleophile is attached to the more substituted carbon of the π -bond. The basis of this regional ectivity is, of course, formation of the more stable tertiary carbocation **326**, which is attacked by bromide ion to give 1-bromo-1-methylcyclohexane (337). This is the normal course of all reactions with acid and an alkene if the intermediate is a cation. Another example was shown in section 2.6.B.ii, where **128** reacted with HCl to give a tertiary carbocation rather than a primary carbocation.



In the reaction of unfunctionalized alkenes with acids such as HX, the key to predicting the regiochemistry is to identify the more stable cation (or radical) intermediate. The presence

^{264.} Markovnikoff, V. Compt. Rend. 1875, 81, 668.

^{265.} Isenberg, N.; Grdinic, M. J. Chem. Educ. 1969, 46, 601.

of a functional group or a heteroatom substituent can led to a different outcome. HBr reacted with the conjugated π bond of methyl acrylate to give methyl 3-bromopropanoate (**339**) as the final product, an anti-Markovnikov addition.²⁶⁶ This result can be predicted by comparing the possible cation intermediates. Addition of H⁺ to the π bond generates cation **338** as the precursor to **339**. Addition to give the alternative cation (**340**), although more substituted would place the positive charge adjacent to a δ^+ carbon of the carbonyl. Such an intermediate is destabilized and is not formed under these conditions. The greater stability of **338** relative to **340** predicts the preference for the observed product **339**.

$$\begin{bmatrix} - CO_2Me \\ + 340 \end{bmatrix} \xrightarrow{CO_2Me} \xrightarrow{HBr} \begin{bmatrix} + CO_2Me \\ 0^{\circ}C \end{bmatrix} \xrightarrow{+ Br} \xrightarrow{CO_2Me} \xrightarrow{Br} \xrightarrow{CO_2Me} \xrightarrow{339}$$

In all cases the carbocation mechanism for addition of acids such as HX to an alkene gives the more stable carbocation, and the substitution product will result from trapping that carbocation with the nucleophile. Many of these intermediate cations are, of course, subject to rearrangement as seen with S_N1 reactions in sec. 2.6.B.ii.

The disconnection for carbocation addition with strong acids HX is:



If we want to prepare an anti-Markovnikov halide from an alkene, we must change the mechanism of the reaction so there is no intermediate carbocation. The new route presented below is more-or-less specific for the reaction of HBr with alkenes. Reaction of methylcyclohexene with HBr, in the presence of the radical initiator *azobis*-isobutyronitrile (AIBN, sec. 13.3), gave the less substituted bromide. This regiochemical outcome immediately showed that the reaction cannot proceed by a cation intermediate, and mechanistic work has shown that it proceeds by a radical intermediate. Alternatively, reaction of an alkene with HBr in the presence of a peroxide leads to the same outcome, also via a radical intermediate (secs. 13.3-13.7). Formation of a radical from AIBN or a peroxide is followed by reaction with HBr (before reaction with the alkene) to generate a bromine radical (Br'). This highly reactive intermediate is attacked by the π -bond of methylcyclohexene to give the more stable carbon radical (**341**).²⁶⁵ This mechanism demands that the bromine atom is added to the C=C unit before the hydrogen atom (contrast with the carbocation reaction where the acidic hydrogen atom added first to form **336**). In the example at hand, methylcyclohexene reacts with the bromide radical to generate the more stable tertiary radical (**341**) with Br on the secondary carbon.

^{266.} Mozingo, R.; Patterson, L.A. Org. Synth. Coll. Vol. 3 1955, 576.



The tertiary radical is formed preferentially rather than the less stable secondary radical where the Br would be on the tertiary carbon. Formation of the more stable radical can be rationalized by essentially the same arguments used for stating that a tertiary cation is more stable than a secondary cation. In the final step of this mechanism, carbon radical intermediate **341** removes a hydrogen atom from HBr to give the final product (1-bromo-2-methylcyclohexane, **342**), and also generate a new bromine radical in a chain propagation step. The net result is addition of H and Br, but the bromine resides on the less substituted position of the double bond. This regiochemical outcome is referred to as **anti-Markovnikov addition**.²⁶⁵ This particular transformation is limited to HBr since HCl and HI do not show such selectivity. Radical addition of HBr to alkenes requires initiation by exposure to light in the presence of a peroxide or another radical initiator such as AIBN (see sec. 13.3).²⁶⁴ Despite these limitations, the reaction can be quite useful in synthesis. Photolysis of **343** with HBr, for example, gave a 73% yield of primary bromide **344** in Coates and co-worker's synthesis of cameroonanol-7 α -ol.²⁶⁷



2.10.B π -Bonds as Lewis Bases: Oxymercuration

As mentioned in previous sections, carbocation intermediates are subject to rearrangement to a more stable ion (sec. 2.6.B.iii). Rearrangement can be minimized or sometimes prevented altogether by attaching a heteroatom to the electrophilic carbon. An example is the oxygenstabilized cation (**345**) generated by reaction of a ketone with an acid catalyst. The electrons on the heteroatom are donated to the positive center leading to resonance stabilization (this is called back donation). Such a cation is typically more stable than the non-oxygen stabilized secondary or tertiary cations that would result after a rearrangement. In this case, rearrangement does not occur. The presence of some Lewis acids adjacent to the carbocation, such as the mercuric ion, stabilizes the cation via back-donation from the metal to the positive center.

^{267.} Davis, C.E.; Duffy, B.C.; Coates, R.M. J. Org. Chem. 2003, 68, 6935.

$$\begin{array}{c} \bullet_{O} \bullet & & \\ & \downarrow \\ R & R \end{array} \xrightarrow{+ H^{+}} \left[\begin{array}{c} \bullet_{O}^{+} \cdot H \\ & \bullet_{O}^{-} \cdot H \\ & R & R \end{array} \xrightarrow{+ H^{+}} R \end{array} \right]$$

In the case of mercury, a bridge-like intermediate such as that depicted in 347 represents the back-donation from the metal atom. The reaction of norbornene (346) and mercuric acetate [Hg(OAc)₂] generated **347**, which reacted with water to give **348**. This cation does not undergo the normally facile norbornyl rearrangement (sec. 12.2.B), indicating the stability imparted by back-donation from the adjacent mercury. Indeed, mercury-stabilized cations are remarkably free of the rearrangements that plague reactions where the cation is generated by other means.²⁶⁸ Despite the stabilization, the cation readily reacts with a suitable nucleophile. In the reaction of 347, water is the reaction medium and also serves as a nucleophile, leading to mercuric alcohol 348. The mercury is removed from 348 by reduction with sodium borohydride to give the final alcohol product. 349 via hydrogenolysis (cleavage of the C-Hg bond, see sec. 4.4.A and 4.8.E).²⁶⁹ This overall process is known as **oxymercuration-demercuration**.²⁷⁰ This reaction usually proceeds with high regioselectivity for the product, with the hydroxyl at the more substituted position (the norbornyl structure also leads to formation of >99% exo alcohol in 349) as observed in reactions of any other cation. In a synthesis of guaiane by Deprés and co-workers,²⁷¹ **350** was treated with mercury (II) bistrifluoroacetate (trifluoroacetate ion is a weak nucleophile and less prone to competitive substitution reactions) to give alcohol 351 after reduction with sodium borohydride. The reaction can be stereoselective, but it is not stereospecific.



- 268. (a) Brown, H.C.; Lynch, G.J. J. Org. Chem. 1981, 46, 930; (b) Brown, H.C.; Geoghegan, Jr., P.J.; Kurek, J.T. Ibid 1981, 46, 3810; (c) Thies, R.W.; Boop, J.L.; Schiedler, M.; Zimmerman, D.C.; LaPage, T.H. Ibid 1983, 48, 2021.
- 269. Brown, H.C.; Kawakami, J.H.; Ikegami, S. J. Am. Chem. Soc. 1967, 89, 1525.
- (a) Kitching, W. Organomet. React. 1972, 3, 319 [Chem. Abstr. 77:87189 1972], (b) Idem. Organomet. Chem. Rev. 1968, 3, 61 [Chem. Abstr. 69:18335x 1968].
- 271. Coquerel, Y.; Greene, A.E.; Deprés, J.-P. Org. Lett. 2003, 5, 4453.

The use of an alcohol rather than water as the nucleophilic solvent will lead to formation of an ether, and is a simple variation of oxymercuration.^{269,272} In Donaldson and Greer's synthesis of the C3-C15 segment of phorboxazole, pyrone **352** was treated with mercuric acetate in methanol.²⁷³ Subsequent reduction with sodium cyanoborohydride (sec. 4.5.D) gave a 69% yield of **353**. The intramolecular variation of this reaction is quite useful, as illustrated by Hiemstra and co-worker's conversion of **354** to **355** in 88% yield, as part of a synthesis of ent-gelsedine.²⁷⁴ When an alkyne is the reactive substrate, oxymercuration leads to a ketone. In a synthesis of (+)-leucascandrolide A by Paterson and Tudge,²⁷⁵ alkyne **356** reacted with mercuric acetate and *p*-toluenesulfonic acid in wet THF to give an 86% yield of methyl ketone **357**. Oxymercuration of terminal alkynes is a valuable route to methyl ketones.



The functional group transform for this reaction type is shown.



2.10.C. π -Bonds as Lewis Bases: Reaction With Dihalogens and Related Reagents

The previous section discussed the reaction of alkenes as Lewis basses with mercuric compounds, which are Lewis acids. Alkenes also react with other Lewis acids, including

^{272.} Coxon, T.M.; Hartshorn, M.P.; Mitchell, J.W.; Richards, R.E. Chem. Ind., 1968, 652.

^{273.} Greer, P.B.; Donaldson, W.A. Tetrahedron Lett. 2000, 41, 3801.

^{274.} van Henegouwen, W.G.B.; Fieseler, R.M.; Rutjes, F.P.J.T.; Hiemstra, H. J. Org. Chem. 2000, 65, 8317.

^{275.} Paterson, I.; Tudge, M. Angew. Chem. Int. Ed. 2003, 42, 343.

dihalogens. Symmetrical reagents such as bromine or chlorine are not normally polarized but the halogens are *polarizable*, and when brought into proximity with a π bond a dipole is induced in the X-X bond [C=C \rightarrow X⁺X⁻]. This type of structure is sometimes called a charge transfer complex. The polarized halogen reacts as a Lewis acid in the presence of an alkene where electron donation from the π -bond to X⁺ leads to displacement of X⁻ and formation of a new C–X bond. This reaction should generate a positive center adjacent to the newly formed C–X bond, but the X group contains unshared electrons that are back donated to the developing positive center, forming a symmetrically bridged (three membered ring) intermediate. The three-membered ring intermediate is called a **halonium ion** (chloronium, bromonium or iodonium). This experimental observation suggests that the three-membered ring intermediate is more stable than the carbocation. Molecules that are not polarizable, such as diatomic hydrogen, do not react in this way. Indeed, dihydrogen requires the presence of a transition metal to first break the H–H bond before it can react with a π -bond.

Evidence suggests that formation of a three-membered ring intermediate is *not* a stepwise process in aprotic solvents. Subsequent $S_N 2$ type attack by the X⁻ gegenion (i.e., backside attack) gives the final addition product, a *vicinal* dihalide. Therefore, reaction with diatomic bromine gives a dibromide, diatomic chlorine gives a dichloride, and diatomic iodine gives a diiodide. Reaction of a diatomic halogen with an alkene in this manner gives the trans (anti) dihalide. Anti-addition of X⁻ (backside attack) at the carbon of the halonium ion intermediate, which is a rigid ion, gives facial selectivity during attack of the nucleophilic X⁻ species and a trans product.

Addition of halogens (X_2) to alkenes is diastereospecific. To explain the specificity for the trans product, initial addition of dihalogen leads to the three-membered halonium ion. Subsequent attack by X⁻ will occur to minimize electronic and steric repulsion. Therefore, addition of diatomic chlorine to cis-3-hexene leads to chloronium ion intermediate 358, and displacement by chloride ion gives the product **359**. Similarly, addition of diatomic bromine to cyclohexene leads to **360** as an intermediate, and anti-attack by bromide ion gives **361**. These two simple examples are typical for the reaction of diatomic halogen and alkenes. The trans relationship easy to see in 361. In reactions of acyclic alkenes such as *cis*-3-hexene, the trans addition of the chlorine atoms to give **359** is more difficult to see when the product is drawn in the typical *zig-zag* drawing that represents the all-anti conformation. In a stereochemically pure alkene such as *cis*-3-hexene, the positions of the ethyl groups and the chlorine atom are fixed. Once the three-membered ring is formed, rotation is also impossible, so the positions of those groups and atoms remain fixed. Subsequent anti-attack by the chloride ion fixes all stereocenters in the final product, and the overall reaction is diastereospecific. The trans addition of the chlorine atoms is clear in the dichloride product 359, where the relative positions of all groups and atoms is retained from the starting alkene, but rotation about that C-C bond is possible, and the molecule is redrawn in the extended conformation marked svn (sec. 1.4.B).²⁷⁶ Note, however, that the stereochemical relationship of the two chlorine atoms refers to anti addition although it

^{276.} Masamune, S.; Ali, Sk.A.; Snitman, D.L.; Garvey, D.S. Angew. Chem. Int. Ed. 1980, 19, 557.

is drawn in the syn conformation. In Boeckman and co-worker's synthesis of (+)-tetronolide,²⁷⁷ vinyl ether **362** reacted with bromine in dichloromethane at –78°C gave **363** in near quantitative yield. There are practical problems when using liquid bromine, and alternative brominating reagents are now available, including tribromide derivatives. Tribromide reagents that have been used for brominating alkenes, and also benzene derivatives, include tetrabutylammonium tribromide,²⁷⁸ 1,8-diazabicyclo-[5.4.0]-undec-7-ene hydrogen tribromide [DBU–H•Br₃]²⁷⁹ (see **21**), cetyltrimethylammonium tribromide,²⁸⁰ and pyridinium bromide perbromide (Py–H•Br₃).²⁸¹ In a synthesis of latrunculin B,²⁸² Fürstner and co-workers treated alkene **364** with 4-dimethylaminopyridinium bromide perbromide (pyridinium tribromide, **365**), and obtained an 87% yield of **366**.



The diastereoselectivity that arises from the intermediacy of a halonium ion has been exploited in a new type of reaction that produces lactones. When an alkene contains a carboxylic acid unit

- 279. Muathen, H.A. J. Org. Chem. 1992, 57, 2740.
- 280. Kajigaeshi, S.; Kakinami, T.; Tokiyama, H.; Hirakawa, T.; Okamoto, T. Chem. Lett. 1987, 627.
- 281. Fieser, L. F.; Fieser, M. Reagents for Organic Synthesis, Wiley: New York, 1967, Vol. 1, p 967.
- 282. Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J.T. Angew. Chem. Int. Ed. 2003, 42, 5358.

^{277.} Boeckman, Jr., R.K.; Shao, P.; Wrobleski, S.T.; Boehmler, D.J.; Heintzelman, G.R.; Barbosa, A.J. J. Am. Chem. Soc. 2006, 128, 10572.

^{278. (}a) Buckels, R.E.; Popov, A.I.; Zelezny, F.; Smith, R.J. J. Am. Chem. Soc. 1951, 73, 4525; (b) Chaudhuri, M.K.; Khan, A.T.; Patel, B.K.; Dey, D.; Kharmawophlang, W.; Lakshmipradha, T.R.; Mandal, G.C. Tetrahedron Lett. 1998, 39, 8163.

elsewhere in the molecule (such as **367**) reaction with diatomic iodine and sodium bicarbonate gives an iodonium ion such as **368**, which is opened by the carboxylate anion to give an iodo-lactone (**369**),¹⁶ diastereoselectively. This reaction is commonly referred to as **iodolactonization**,²⁸³ and it can be applied to acyclic systems as well.²⁸⁴ In a synthesis of (–)-cinatrin B by Rizzacasa and co-workers,²⁸⁵ alkene-acid **370** formed iodonium-carboxylate **371** during the course of the reaction with iodine and sodium bicarbonate, leading to a 97% yield of **372** (88% ds). A variation of this cyclization reaction uses an ester. In a synthesis of (+)-epoxyquinol A,²⁸⁶ Hayashi and co-workers treated ester **373** with iodine, and obtained an 81% yield of **374** (>99% ee after crystallization). Several approaches have been developed for asymmetric iodolactonization reactions.²⁸⁷ Both bromolactonization and chlorolactonization reactions are known. The use of liquid bromine or gaseous chlorine can be problematic, but as mentioned above, pyridinium bromide perbromide in THF, can be used to generate bromolactones.²⁸⁸



⁽a) Klein, J. J. Am. Chem. Soc. 1959, 81, 3611; (b) van Tamelen, E.E.; Shamma, M. Ibid 1954, 76, 2315;
(c) House, H.O.; Carlson, R.G.; Babad, H. J. Org. Chem. 1963, 28, 3359; (d) Corey, E.J.; Albonico, S.M.; Koelliker, V.; Schaaf, T.K.; Varma, R.K. J. Am. Chem. Soc. 1971, 93, 1491.

- 285. Cuzzupe, A.N.; Di Florio, R.; Rizzacasa, M.A. J. Org. Chem. 2002, 67, 4392.
- 286. Shoji, M.; Yamaguchi, J.; Kakeya, H.; Osada, H.; Hayashi, Y. Angew. Chem. Int. Ed. 2002, 41, 3192.
- 287. (a) Blot, V.; Reboul, V.; Metzner, P. J. Org. Chem. 2004, 69, 1196; (b) Moon, H.-S.; Eisenberg, S.W.E.; Wilson, M.E.; Schore, N.E.; Kurth, M.J. J. Org. Chem. 1994, 59, 6504; (c) Haas, J.; Piguel, S.; Wirth, T. Org. Lett. 2002, 4, 297; (d) Wang, M.; Gao, L.X.; Mai, W.P.; Xia, A.X.; Wang, F.; Zhang, S.B. J. Org. Chem. 2004, 69, 2874.
- 288. For an example taken from a synthesis see Trost, B.M.; Haffner, C.D.; Jebaratnam, D.J.; Krische, M.J.; Thomas, A.P. J. Am. Chem. Soc. 1999, 121, 6183.

^{284. (}a) Cardillo, G.; Orena, M. *Tetrahedron* **1990**, *46*, 3321; (b) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681.

Iodolactamization is possible via a related process, but problems relating to the bidentate nature of amide anion require modification of conditions, as illustrated by formation of the lactone as the major product in a previous study.^{287a} Knapp and Rodriques described a synthesis in which amide **375** was first converted to the corresponding triflate, and subsequent reaction with iodine gave iodo-lactam **376** in 68% yield.²⁸⁹ When a chiral oxazolidine auxiliary was attached to the nitrogen, iodolactamization occurred with excellent enantioselectivity.²⁹⁰ A related cyclization of *N*-sulfonyl-amino-alkenes and NBS gave the bromolactam,²⁹¹ and a dichloro-*N*,*N*-bis(allyl) amide was converted to a dichlorolactam with FeCl₂.²⁹²



Another addition involves the reaction of unfunctionalized alkenes with aqueous solutions of bromine or chlorine. Halogenation can proceed by formation of a cation under aqueous conditions, but the course of the reaction is complicated by the fact that dissolution of chlorine or bromine in water results in formation of a hypohalous acid (XOH, X = Cl, Br), represented by the reaction:

 X_2 + HOH \longrightarrow X-OH = X⁺-OH

When pure XOH (ClOH or BrOH) is used in an aprotic medium, the X⁺ portion of this reagent is electrophilic and reacts with an alkene to generate the same halonium ion observed with bromine and chlorine additions. The ⁻OH gegenion is the nucleophilic partner and opens the halonium ion to produce a halohydrin, analogous to the reactions of bromine or chlorine. It is more typical for these reagents to be generated in water, however, and the initially formed halohydrin will exist primarily as the ring-opened cation or an ion pair, and the hydroxide nucleophile generally attacks the cationic center to give the more substituted alcohol.²⁹³ Indeed, with relatively simple systems, reactions of alkenes with aqueous chlorine or bromine usually give the halohydrin with the hydroxyl at the *more* substituted position.^{283,293} Reaction of methylcyclohexene with HOCl in water, for example, gives the usual Markovnikov product, chlorohydrin (**377**).



^{289.} Knapp, S.; Rodriques, K.E.; Levorse, A.T.; Ornaf, R.M. Tetrahedron Lett. 1985, 26, 1803.

293. Boguslavskaya, L.S. Russ. Chem. Rev. 1972, 41, 740.

^{290.} Shen, M.; Li, C. J. Org. Chem. 2004, 69, 7906.

^{291.} Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. Tetrahedron Lett. 1984, 25, 1063.

^{292.} Tseng, C.K.; Teach, E.G.; Simons, R.W. Synth. Commun. 1984, 14, 1027.

Reaction of NBS or NCS with a minimal amount of H₂O in DMSO is a convenient method for the preparation of HOBr or HOCl, respectively.²⁹⁴ Subsequent reaction with an alkene leads to a chlorohydrin or a bromohydrin. The reaction is usually selective for the trans product, and this suggests the presence of the halonium ion intermediate. This reaction is one that can be mechanistically ambiguous in some cases since the outcome depends on the solvent, the nature of the substrate, and the concentration of the reagents. A synthetic illustration of this reaction is addition of hypobromous acid (formed in aqueous solution with NBS) to **378**, taken from Elango and Yan's synthesis of (+)-narciclasine.²⁹⁵ This reaction generated a 1:1 mixture of the two regioisomers, **379** and **380**, each having the trans-geometry shown. Although some halohydrins are formed with good regioselectivity, this example shows that one should anticipate a mixture in the absence of regiocontrolling factors.



These reactions give the useful transform:

2.11. FUNCTIONAL GROUP MANIPULATION BY REARRANGEMENT

There are several common functional group manipulations that involve skeletal rearrangement. This section will discuss a few examples that correlate with Named reactions, both to illustrate the principle and to show the details of these specific transformations.

2.11.A. Beckmann Rearrangement

Oximes (381) are readily obtained by reaction of aldehydes or ketones with hydroxylamine. When oximes are treated with sulfuric acid, PCl_5 and related reagents, rearrangement occurs to

 ⁽a) Dalton, D.R.; Hendrickson, J.B.; Jones, D. Chem. Commun. 1966, 591; (b) Dalton, D.R.; Dutta, V.P., J. Chem. Soc. B 1971, 85; (c) Sisti, A.J. J. Org. Chem. 1970, 35, 2670.

^{295.} Elango, S.; Yan, T.-H. J. Org. Chem. 2002, 67, 6954
give substituted amides in what is called the **Beckmann rearrangement**.²⁹⁶ Initial protonation of the hydroxyl group to give **382** is followed by rearrangement, with displacement of water to give **383**. Subsequent reaction with water and loss of a proton yields the amide.²⁹⁷ The group that migrates is generally the one anti to the hydroxyl, and this is often used as a method of determining the configuration of the oxime. However, the syn group may migrate in some oximes, especially where R and R' are both alkyl. In most cases however, it is likely that the oxime undergoes isomerization under the reaction conditions *before* migration takes place.²⁹⁸ It is possible to get mixtures of the two different amides from oximes derives from unsymmetrical ketones. Note that hydrogen seldom *migrates*, and most alkyl groups are compatible with the reaction. In alkyl aryl ketones, the aryl group generally migrates preferentially. The oximes of a cyclic ketones such as **384** give ring enlargement under these conditions, with formation of a lactam (**385**).²⁹⁹ Beckmann rearrangements have also been carried out photochemically.³⁰⁰



Esters of oximes also undergo the Beckmann rearrangement with many organic and inorganic acids. A side reaction with many substrates is the formation of nitriles. Under the correct conditions, cycloalkane carboxylic acids rearrange to form lactams. Azacyclododecan-2-one, for example, was prepared from cycloundecan-2-carboxylic acid by reaction with nitrosyl sulfuric acid in chlorosulfonic acid.³⁰¹ Another useful variation of the Beckmann rearrangement is the direct treatment of a ketone with hydroxylamine-*O*-sulfonic acid in the presence of an acid such as formic acid, or with sulfuric acid in a second step. Initial formation of the oxime-

- 297. Donaruma, L.G.; Heldt, W.Z. Org. React. 1960, 11, 1, see p. 5.
- 298. Lansbury, P.T.; Mancuso, N.R. Tetrahedron Lett. 1965, 2445.
- 299. Vinnik, M.I.; Zarakhani, N.G. Russ. Chem. Rev. 1967, 36, 51.
- 300. (a) Izawa, H.; de Mayo, P.; Tabata, T. *Can. J. Chem.* 1969, 47, 51; (b) Cunningham, M.; Ng Lim, L.S.; Just, T. *Can. J. Chem.* 1971, 49, 2891; (c) Suginome, H.; Yagihashi, F. J. *Chem. Soc. Perkin Trans.* 1 1977, 2488.

^{296.} For reviews, see (a) Gawley, R.E. Org. React. 1988, 35, 1; McCarty, C.G. in Patai The Chemistry of the Carbon-Nitrogen Double Bond, Wiley: NY, 1970, pp. 408-439; (b) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-7; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 80-81. Also see (d) Nguyen, M.T.; Raspoet, G.; Vanquickenborne, L.G. J. Am. Chem. Soc. 1997, 119, 2552.

^{301. (}a) Imperial Chemical Industries LTD Belgian Patent 616 544, Oct 17 1962 [*Chem . Abstr.* 1963, 59:452];
(b) Nagasawa, H.T.; Elberling, J.A.; Fraser, P.S.; Mizuno, N.S. *J. Med. Chem.* 1971, 14, 501.

O-sulfonic acid (**387**) is followed by *in situ* formation of an oxime, which rearranges in the presence of the acid.³⁰² In the example shown, 2-pentylcyclohexanone (**386**) reacted with hydroxylamine-*O*-sulfonic acid and formic acid to give **387**, and rearrangament *in situ* gave a 71% yield of 7-pentyl-hexahydroazepin-2-one, **388**.³⁰³



A synthetic example, illustrating another variation in the Beckmann rearrangement, is taken from the Denis and Agouridas synthesis of the ketolide analog of 6-*O*-methylazithromycin.³⁰⁴ Studies related to the synthesis of the targeted compound generated oxime **389**, which was treated with tosyl chloride to give the *O*-tosyl oxime. Subsequent Beckmann rearrangement gave lactam **390** in 70% yield. It is clear from this example that variations of the Beckmann rearrangement that do not use strong acid are compatible with a vast array of functionality.



2.11.B. Schmidt Rearrangement

The addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and alkenes all give amides, and all go by the name **Schmidt reaction**.³⁰⁵ The reaction with carboxylic acids is probably the most common, involving initial formation of an acyl azide (**391**), which rearrangements with loss of nitrogen to give a transient isocyanate (**392**).

^{302. (}a) Smith, P.A.S. J. Am. Chem. Soc. 1948, 70, 323; (b) Sanford, J.K.; Blair, F.T.;. Arroya, J.; Sherk, E.W. J. Am. Chem. Soc. 1945, 67, 1941.

^{303.} Duhamel, P.; Kotera, M.; Monteil, T.; Marabout, B.; Davoust, D. J. Org. Chem. 1989, 54, 4419.

^{304.} Denis, A.; Agouridas, C. Bioorg. Med. Chem. Lett. 1998, 8, 2427.

^{305. (}a) Banthorpe, D.V. in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, 1971, pp. 405-434; (b) *The Merck Index, 14th Ed.* Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-83; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd Ed.* Wiley-Interscience, New Jersey, 2005, pp. 574-575.

Subsequent reaction with water gives **393**, which decarboxylates to give the amine product.³⁰⁶ Sulfuric acid and many Lewis acids can be used as catalysts in this reaction. Under normal reaction conditions, the isocyanate is not isolated. When hydrazoic acid reacts with a ketone, the product of the rearrangement is an amide (**394**).³⁰⁷

$$\begin{array}{c} O \\ R \\ HN_{3}, H^{+} \\ OH \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{-} \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3}, H^{+} \\ \end{array} \begin{array}{c} O \\ R \\ \end{array} \begin{array}{c} O \\ HN_{3} \\ \end{array} \begin{array}{c} HN_{3} \\ HN_{3} \\ HN_{3} \\ \end{array} \begin{array}{c} O \\ HNR \\ HNR \\ \end{array} \begin{array}{c} O \\ HNR \\ \end{array} \begin{array}{c} O \\ HNR \\ HNR \\ \end{array} \begin{array}{c} O \\ HNR \\ HNR \\ HNR \\ \end{array} \begin{array}{c} O \\ HNR \\ HNR$$

Dialkyl ketones and cyclic ketones tend to react faster than alkyl aryl ketones, and these faster than diaryl ketones. Cyclic ketones give lactams,³⁰⁸ and a simple example is the reaction of cyclohexanone with HBr and sodium azide. A 63% yield of hexahydroazepine-2-one (**395**) was obtained in water, and a 66% yield was obtained in acetic acid (HBr, NaNO₂).³⁰⁹ A variation of the Schmidt reaction treated the ketone with hydrazoic acid with another acid and also obtained a lactam. Under these conditions 2-isopropylcyclopentanone reacted with HN₃/ H_2SO_4 at 3-7°C to give a 63% yield of 6-isopropyl-2-piperidone, **396**.³¹⁰



The reaction is rarely applied to aldehydes, where the product is usually a nitrile. Nitriles are observed as by-products with ketones as well. Regioselectivity can be problem when unsymmetrical cyclic ketones are converted to the lactam, but the reaction often proceeds with good regioselectivity. When 2-methyl-cyclohexanone reacted with sodium azide in the presence of polyphosphoric acid,³¹¹ For example, the two lactam products were 7-methylhexahydroazepin-2-one (**397**) in 54% yield and **398** in 10% yield.³¹² A useful variation

- 309. Smith, P.A.S. J. Am. Chem. Soc. 1948, 70, 320-323.
- 310. Shechter, H.; Kirk, J.C. J. Am. Chem. Soc. 1951, 73, 3087.
- 311. Conley, R.T. J. Org. Chem. 1958, 23, 1330.
- 312. Overberger, C.G.; Parker, G.M. J. Polym. Sci., A-1968, 6, 513.

^{306.} Koldobskii, G.I.; Ostrovskii, V.A.; Gidaspov, B.V. Russ. Chem. Rev. 1978, 47, 1084.

Koldobskii, G.I.; Tereschenko, G.F.; Gerasimova, E.S.; Bagal, L.I. Russ. Chem. Rev. 1971, 40, 835; (b) Beckwith, A.L.J. in Zabicky, J. The Chemistry of Amides, Wiley, NY, 1970, pp. 137-145.

^{308.} Krow, G.R. Tetrahedron 1981, 37, 1283.

of the Schmidt reaction involves reaction of a silyl enol ether of a cyclic ketone with TMSN₃,³¹³ followed by photolysis of the product with UV light to give a lactam.

Asynthetic example illustrates an intramolecular variation. In a synthesis of (+)-aspidospermidine by Aubé and co-workers, ketone **399** (containing the alkyl azido substituent shown) was treated with TiCl₄,³¹⁴ leading to the intramolecular Schmidt reaction that gave lactam **400** in 82% yield.



2.11.C. Related Rearrangements

An intermediate in the Schmidt rearrangement was an acyl azide **391**, and the intermediate isocyanate **392** was not isolated under those conditions. Without the aqueous conditions, the thermal rearrangement of acyl azides to isocyanates is known as the **Curtius rearrangement**.³¹⁵ Subsequent reaction with water, alcohols or amines lead to amines, carbamates, or acylureas.³¹⁶ In general, acyl azides are prepared by treatment of acylhydrazines (hydrazides) with nitrous acid. Lewis acids can catalyze the Curtius rearrangement, but they are not required. In a synthesis of (+)-yatakemycin by Boger and co-workers,³¹⁷ acid **401** was treated with diphenyl phosphoryl azide (DPPA) to give the acyl azide, **402**. Under the aqueous conditions, the product was amine **403**, via reaction of water with the intermediate isocyanate.



^{313.} Evans, P.A.; Modi, D.P. J. Org. Chem. 1995, 60, 6662.

^{314.} Iyengar, R.; Schildknegt, K.; Morton, M.; Aube, J. J. Org. Chem. 2005, 70, 10645.

^{315. (}a) Banthorpe, D.V. in Patai, S. *The Chemistry of the Azido Group*; Wiley, NY, 1971, pp. 397-405; (b) The MerckIndex, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-21 (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd Ed.* Wiley-Interscience, New Jersey, 2005, pp. 192-193.

^{316. (}a) Pfister, J.R.; Wyman, W.E. Synthesis 1983, 38. See also (b) Capson, T.L.; Poulter, C.D. Tetrahedron Lett. 1984, 25, 3515.

^{317.} Tichenor, M.S.; Kastrinsky, D.B.; Boger, D.L. J. Am. Chem. Soc. 2004, 126, 8396.

When an amide is treated with sodium hypobromite (NaOBr; NaOH and Br₂) an isocyanate is formed,³¹⁸ and subsequent hydrolysis liberates an amine with one less carbon that the starting amide, in what is known as the **Hofmann rearrangement**.³¹⁹ Ureas and acylureas are sometimes formed in this reaction. *N*-Acyl derivatives of hydroxamic acids³²⁰ give isocyanates when treated with base, or upon heating, in the **Lossen rearrangement**.³²¹ Similarly, aromatic acyl halides are converted to amines when treated with hydroxylamine-*O*-sulfonic acid.³²²

These reactions give the retrosynthetically useful transforms:

2.12. AROMATIC SUBSTITUTION

In many ways, the principles of substitution, elimination, and addition converge in aromatic systems in what is generically called aromatic substitution.³²³ Addition to electrophilic centers, substitution of carbocations, nucleophilic displacement, and elimination of leaving groups are all mechanistic features of various aromatic substitution reactions.

2.12.A. Defining Aromatic Substitution

The substitution reactions discussed in previous sections occurred at a sp³ hybridized carbon, and direct substitution at a sp² carbon was not observed. Addition reactions, however, occurred at sp² hybridized carbons in the presence of acids. Substitution reactions are possible, but the conditions are much different. If we mix benzene with Cl–Cl at ambient temperature and pressure, for example, there is no reaction. For a substitution reaction to occur benzene must act as a base, but benzene does *not* react with HCl or HBr when they are mixed together so it is clear that it is too weak a base for even these strong acids. Benzene does not react with the polarizable Cl–Cl or Br–Br, indicating that it is too weak a Lewis base as well. Benzene is resonance stabilized, so these results are quite reasonable. The poor reactivity can be changed by reaction of a formal cation (X⁺) with benzene, where benzene is now a strong enough

- 321. Salomon, C.J.; Breuer, E. J. Org. Chem. 1997, 62, 3858.
- 322. Wallace, R.G.; Barker, J.M.; Wood, M.L. Synthesis 1990, 1143.
- 323. For examples see Ref. 3, pp 129-134, 619-629, 703-705, 759-761, 911-912.

^{318.} Sy, A.O.; Raksis, J.W. Tetrahedron Lett. 1980, 21, 2223.

^{319. (}a) Wallis, E.S.; Lane, J.F. Org. React. 1946, 3, 267-306; (b) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-46; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 326-327.

^{320.} Bauer, L.; Exner, O. Angew. Chem. Int. Ed. 1974, 13, 376.

Lewis base to react, forming a new C–X bond as the aromatic ring is disrupted. This process is generalized for the reaction of benzene with an electrophilic species (X⁺), where the cation (404) formed by the reaction is resonance stabilized. Loss of a proton to form 405, in what is essentially an E1 process, is very rapid because a stable aromatic ring will be regenerated. The E1 analogy is reasonable when it recognized that the proton on the carbon adjacent to the cationic center is acidic. O'Ferrall and co-workers have estimated the pK_a of this proton to be about -24.3.³²⁴ The intermediate cation 404A is sometimes referred to as a benzenonium ion³²⁵ but old terminology called it a Wheland intermediate, especially when drawn as the delocalized cation 404B.³²⁶ In this reaction, the electrophilic species (X⁺) replaced an aromatic hydrogen via an electrophilic process, and is termed electrophilic aromatic substitution.³²⁷



Nucleophilic attack on unsubstituted benzene rings is difficult since an electron-rich species must react with an electron-rich substrate. The reaction is possible if a good leaving group is attached to the aromatic ring, but reaction conditions are usually harsh. The reaction of an aryl halide (406) with a nucleophile (Y^-) produces a resonance stabilized anion (407) as an intermediate, but the transition state for the formation of 407 is relatively high in energy and requires high temperatures, high pressures, and long reaction times. The presence of groups on the aromatic substrate that can disperse the charge by resonance, such as nitro groups, stabilize the carbanionic intermediate and the reaction proceeds under much milder reaction conditions. Elimination of X⁻ from 407 gives the final substitution product, 408. The overall reaction is called **nucleophilic aromatic substitution**.



An alternative mechanism leads to nucleophilic aromatic substitution. When an unactivated aryl halide (405) is treated with a strong base, removal of the ortho hydrogen and subsequent loss of the halide ion (X⁻) gives a highly reactive intermediate called a benzyne (409). Benzyne will be attacked by nucleophiles in a reaction that opens the π bond that is not part of the aromatic cloud, to generate a carbanion (410). Protonation completes the sequence to give the

^{324.} McCormack, A.C.; McDonnell, C.M.; More O'Ferrall, R.A.; O'Donoghue, A.C.; Rao, S.N. J. Am. Chem. Soc. 2002, 124, 8575.

^{325.} Stock, M.M. Aromatic Substitution Reactions, Prentice-Hall: Englewood Cliffs, NJ, 1968, p 21.

^{326.} Wheland, G.W. J. Am. Chem. Soc. 1942, 64, 900.

^{327.} Taylor, R. Electrophilic Aromatic Substitution, Wiley, Chichester, 1990.

aromatic substitution product, **411**. The chemistry of benzyne, and arynes in general, is more than 100 years old,³²⁸ and these reactive intermediates remain quite important in a variety of synthetic transformations.³²⁹



Section 2.11.B will deal with the most fundamental aromatic substitution reactions. This subject is usually presented in detail in undergraduate textbooks. The treatment varies greatly with the text, however, and leading references are usually absent. This discussion is intended only as a brief review.

2.12.B. Electrophilic Aromatic Substitution

The π bonds in benzene are poor electron donors because, in part, such a reaction would disrupt the stable aromatic sextet. In other words, benzene is a weak base and normally will not react with an electrophilic species such as HCl, as mentioned above. Although benzene can form a weak charge transfer complex with chlorine (see **412**), mixing benzene and chlorine does *not* give a substitution reaction. When a strong Lewis acid such as AlCl₃ is added, however, a charge transfer complex such as **413** is formed *between the Lewis acid and chlorine rather than with benzene*. In this complex, the chlorine-chlorine bond is weakened sufficiently so that it can be attacked by benzene, transferring one chlorine to benzene (with disruption of the aromatic system) and transfer of the other chlorine to AlCl₃ (see **414**). For all practical purposes, **413** can be treated as Cl⁺ in its reaction with benzene. The stronger the Lewis acid (see sec. 2.3), the faster the halogen and benzene react. The result is formation of a Wheland intermediate, which loses a proton to give chlorobenzene.³³⁰ It is important to note that the charge-transfer complex mechanism may not be valid for chlorination of alkyl benzenes and is solvent dependent.^{330a}



Two charge-transfer complexes are formed during the course of this reaction.³³¹ The first will be **413** and the second (**414**) is generated during loss of the proton in the aromatization

^{328.} Stoermer, R.; Kahlert, B. Ber. Dtsch. Chem. Ges. 1902, 35, 1633.

^{329.} Wenk, H.H.; Winkler, M.; Sander, W. Angew. Chem. Int. Ed. 2003, 42, 502.

^{330. (}a) de la Mare, P.B.D. Acc. Chem. Res. 1974, 7, 361 and references cited therein; (b) Le Page, L.; Jungers, J.C. Bull. Soc. Chim. Fr. 1960, 525; (c) Olah, G.A.; Kuhn, S.J.; Hardie, B.A. J. Am. Chem. Soc. 1964, 86, 1055.

^{331.} Reference 325, p 27.

process. In the chlorination reaction, the rate-determining step (the slowest) is conversion of the charge transfer complex to the Wheland complex (**413** \rightarrow complex).³²⁷ Formation of **413**, conversion of the Wheland complex to **414**, and elimination of the proton are all fast processes. Bromine reacts in a manner identical to chlorine,^{332,330b} producing Br⁺ as a reactive intermediate (in the charge-transfer complex). Reaction of bromine, benzene, and aluminum chloride gives bromobenzene. Typical Lewis acid catalysts for this reaction are iodine, AlCl₃, SbCl₃, PCl₃, PCl₅, and SnCl₄.³³³ When benzene is treated with a mixture of nitric and sulfuric acids, nitrobenzene is the product,³³⁴ via a nitronium ion (NO₂⁺).³³⁵ Benzene also reacts with sulfuric acid [or sulfuric acid saturated with sulfur trioxide (SO₃), which is known as fuming sulfuric] to give benzenesulfonic acid.³³⁶ Benzenesulfonic acid is also formed by reaction of benzene with chlorosulfonic acid (ClSO₃H)³³⁷ or fluorosulfonic acid (FSO₃H).³³⁸

When substituents are present on the aromatic ring, these substitution reactions can proceed with great selectivity. Majetich and co-workers, for example, showed that aniline reacted with HBr/DMSO to give a 76% yield of 4-bromoaniline, in a remarkably selective reaction.³³⁹ Bromination of **415** gave a 75% yield of **416**³⁴⁰ in a synthesis of lateriflorone by Theodorakis and co-workers. Note that the highly activated ring in **415** was brominated without the use of a Lewis acid. Such reactivity is common when strong activating groups such as OH and OR are present on the aromatic ring. In a synthesis of 11,12-demethoxypauciflorine,³⁴¹ Magnus and co-workers treated **417** with fuming nitric acid, and obtained an 82% yield of **418**.

332. Reference 327, pp 377-380.

- (a) Hoggett, J.G.; Moodie, R.B.; Penton, J.R.; Schofield, K. Nitration and Aromatic Reactivity, Cambridge Univ. Press, Cambridge, 1971; (b) Schofield, K. Aromatic Nitration, Cambridge Univ. Press, Cambridge, 1980.
- 335. (a) Westheimer, F.H.; Kharasch, M.S. J. Am. Chem. Soc. 1946, 68, 1871; (b) Martinsen, H. Z. Phys. Chem. 1905, 50, 385; (c) Idem Ibid 1907, 59, 605; (d) Marziano, N.C.; Sampoli, M.; Pinna, F.; Passerini, A. J. Chem. Soc. Perkin Trans. 2 1984, 1163.
- 336. (a) Brand, J.C.D.; Jarvie, A.W.P.; Horning, W.C. J. Chem Soc. 1959, 3844; (b) Cerfontain, H.; Sixma, F.L.J.; Vollbracht, L. Recl. Trav. Chim. Pays-Bas 1963, 82, 659; (c) Cerfontain, H. Ibid 1961, 80, 296; (d) Idem Ibid 1965, 84, 551
- 337. (a) Harding, L. J. Chem. Soc. 1921, 1261; (b) Levina, L.I.; Patrakova, S.N.; Patruskev, D.A. J. Gen. Chem. USSR 1958, 28, 2427.
- 338. Gillespie, R.J. Acc. Chem. Res. 1968, 1, 202.
- 339. Majetich, G.; Hicks, R.; Reister, S. J. Org. Chem. 1997, 62, 4321.
- 340. Tisdale, E.J.; Li, H.; Vong, B.G.; Kim, S.H.; Theodorakis, E.A. Org. Lett. 2003, 5, 1491.
- 341. Magnus, P.; Gazzard, L.; Hobson, L.; Payne, A.H.; Rainey, T.J.; Westlund, N.; Lynch, V. Tetrahedron 2002, 58, 3423.

^{333. (}a) Price, C.C. J. Am. Chem. Soc. 1936, 58, 2101; (b) Idem Chem. Rev. 1941, 29, 37; (c) Price, C.C.; Arntzen, C.E. J. Am. Chem. Soc. 1938, 60, 2835.



Electrophilic aromatic substitution occurs readily many aromatic derivatives. Naphthalene, for example, reacts with a mixture of bromine and aluminum chloride to give 99% of 1-bromonapthalene (**419**) with only 1% of 2-bromonapthalene (**420**). Substitution at the 1-position of naphthalene is greatly preferred,³⁴² and this can be explained by examining the reactive intermediate. Reaction of naphthalene and Br⁺ at the C1-position generates the resonance stabilized Wheland type intermediate, **421**. There are a total of seven resonance structures in **421**, and an important feature is the presence of a fully aromatic (intact benzene ring) structure in four of those resonance intermediates. Similar analysis of the intermediates for attack at C2 reveals there are six structures, but only two of them have fully aromatic rings. This simple analysis predicts **421** to be more stable than the intermediate resulting from attack at C2, consistent with the experimentally observed major product **419** in a 99:1 ratio (**419/420**).



In aromatic substrates where reaction with X^+ generates several different cationic intermediates that are close in energy, little selectivity is expected and a mixture of products is predicted. An illustration is the nitration reaction of phenanthrene, which gave five products: **422** (6%), **423** (23%), **424** (7%), **425** (27%) and **426** (37%).³⁴³ Although substitution at C9 is preferred, a complex mixture is obtained that may be difficult to separate. Substitution at several positions is a common occurrence for substitution reactions of polycyclic aromatic derivatives, although the product distribution is usually influenced by the nature of the catalyst and by the reaction conditions that are used.

^{342.} Reference 325, p 76.

^{343.} Reference 325, p 78.



MOLECULAR MODELING: Reactive Intermediates Anticipate Selectivity in Nitration of Phenanthrene

According to the *Hammond Postulate*, the geometry of the reactants in an *exothermic* reaction should resemble the geometry of the transition state. This suggests that the relative energies of the intermediates will reflect the relative energies of the transition states connecting them to products, and will anticipate the kinetic product distribution. Consider the electrophilic nitration of phenanthrene. Each of five different products (422-426), follows from a different reactive ("Wheland") intermediate. Of the five products, 423, 425 and 426 account for 87% of the total.

Build the Wheland intermediate that leads to **422** and obtain its energy. Start from *Naphthalene* under the **Rings** menu, and build the third ring from a pair of sp^2 carbons, a carbocation center and an sp^3 carbon. Add *Nitro* (Groups menu) to the sp^3 carbon. In a similar way, obtain energies for the intermediates leading to **423-425**. Before you start each, *click* on > at the right of the tab(s) at the top of the screen and select *Continue* to bring up a fresh builder palette. To build the intermediate leading to **426**, start from *Benzene* (**Rings** menu), add a second benzene to make biphenyl and connect the two rings with an sp^3 carbon and a carbocation center. Add *Nitro* (Groups menu) to the sp^3 carbon. Rank the five Wheland intermediates in order of increasing energy. Are the intermediates sufficiently close in energy (within 5-20 kJ/mol) such that it is reasonable to expect that all five products will actually be observed?

Despite the many products produced in the previous example, electrophilic substitution of aromatic molecules can proceed with great selectivity in many cases. An example is the nitration of benzo[c]fluorene (427), which gave a good yield of the 5-nitro derivative (428).³⁴⁴ Nitration of 2-hydroxyazulene (429) gave a mixture of 1-nitroazulen-2-one (430) and 6-nitro-2-hydroxyazulene (431).³⁴⁵



344. Bolton, R. J. Chem. Soc. (S) 1977, 149.

345. Nozoe, T.; Asao, T.; Oda, M. Bull. Chem. Soc. Jpn. 1974, 47, 681.

Heterocyclic aromatic derivatives also undergo electrophilic aromatic substitution reactions. Pyrrole, for example, reacts with nitric acid in acetic anhydride, at 0°C, to give 50% of 2-nitropyrrole and 15% of 3-nitro-pyrrole. Pyrrole is more reactive in these reactions when compared to benzene, and the mild reaction conditions described are sufficient. One caution is that the products may decompose with prolonged exposure to a powerful Lewis acid. The preference for substitution at C2 in pyrrole is seen in other five-membered ring heterocycles such as furan and thiophene. This preference can be explained by the relative stability of the cationic intermediates, just as in substitution reactions with benzene derivatives. Inspection of the cation resulting from attack at C2 (432) shows that the lone pair electrons on the heteroatom participates in resonance delocalization, giving a total of three resonance structures. Since attack at C3 (see 433) will lead to only two structures, attack at C2 is preferred. If there are substituents at C2 and C5, however, attack will occur at C3. Pyrrole, with the more basic nitrogen atom, is better able to stabilize the cationic intermediate than furan or thiophene and is more reactive.



Pyridine, unlike five-membered ring heterocycles, undergoes substitution with difficulty and at the C3 position. This reaction illustrated by its reaction with mercuric sulfate (HgSO₄) and H_2SO_4 (at 220°C) to give pyridine 3-sulfonic acid. The poor reactivity relative to pyrrole is clear by simply examining the vigorous conditions that are required for the reaction. The preference for C3 substitution in six-membered ring heterocycles is again explained by generation of a more stable cationic intermediate.



Other heterocyclic ring systems react with the reagents in this section, including bicyclic and tricyclic compounds. In some cases, one aromatic ring contains a heteroatom while the other does not, as in quinoline or isoquinoline. The aromatic ring in quinoline (**434**) that does not contain nitrogen undergoes electrophilic aromatic substitution preferentially. It is known that pyridine is less reactive than benzene, so it is reasonable that the pyridine portion of quinoline should also be less reactive than the benzene portion. The two products of this reaction (HNO₃, H₂SO₄, 0°C, 3 min.) are 8-nitroquinoline (**435**) and 5-nitroquinoline (**436**, the nitrogen is 1), formed in roughly equal amounts. The preference for attack at C5 and C8 is explained by the usual stability arguments for the cationic intermediates.

The products arising from nitration of quinoline clearly show that one ring reacted faster than

the other, although the isomer distribution depends on reaction conditions. The deactivated pyridine ring in **434** lowers the rate of electrophilic substitution relative to the other aromatic ring. This general phenomenon can be applied to monocyclic heterocycles, polycyclic heterocycles, polycyclic aromatic hydrocarbons, and benzene derivatives.

The presence of electron-withdrawing or electron-releasing groups on an aromatic ring will deactivate or activate that ring to electrophilic aromatic substitution, which suggests that the primary effect is inductive. It is also true that the inductive effect will be transmitted to or from the aromatic ring at the carbon bearing the substituent, the *ipso* carbon. Reaction of X⁺ with a benzene ring containing an electron-rich substituent leads to a Wheland intermediate that has a negative charge or a δ - dipole attached to the ipso carbon. The expected electron releasing effect will stabilize the cationic intermediate. If we focus only on inductive effects that occur in the reactive intermediates, the effect can be used as a convenient method for predicting reactivity. If the substituent releases electrons (X has a negative charge or a δ - dipole, as in **437**) that substituent is said to have a positive inductive effect (+I) and should stabilize the cation intermediate. A negative inductive effect (-*I*) occurs when the substituent at the ipso carbon is electron withdrawing (Z has a positive charge or δ^+ dipole, as in **438**), and the cation intermediate is destabilized making its formation more difficult.



A second factor is important in electrophilic aromatic substitution reactions. If the group at the ipso carbon is capable of dispersing the positive charge by resonance delocalization, that intermediate will be more stable. This resonance effect is often called a mesomeric effect, and labeled +M or -M. The OR group in 439 exhibits a +M effect since the electrons on oxygen can be donated to the positive charge at the ipso carbon, which results in transferring the charge to oxygen, as shown, by resonance. It is reasonable to assume that a substituent at the ipso carbon with unshared electrons (such as oxygen, sulfur, nitrogen, halogen) will have a +M effect, which will stabilize the cationic intermediate of electrophilic aromatic substitution. Conversely, a group bearing a positive charge or a partially positive dipole will not be able to delocalize a positive charge, and indeed, the two like charges on adjacent atoms will destabilize that intermediate by electronic repulsion, as in 440. An intermediate such as 439 should be easier to form and since cation formation is the rate-determining step (see above), the substitution should be faster. Anisole, for example, is very reactive in electrophilic aromatic substitution, and in many cases a Lewis acid is not required for the reaction. Toluene, on the other hand, has a +I effect (see 441) but no mesomeric effect. The substitution should be faster than for benzene (with no activating substituents) but slower than for anisole with both a + I and a + M effect (see 442).



It is important to note that the +M effect observed with anisole occurs only with ortho and para substitution. In those cases the positive charge in the intermediate can be transferred to the ipso carbon and thereby to the oxygen. The presence of an extra resonance form is indicative of increased stability for those intermediates because delocalization occurs over more atoms. This greater stability means that the cation is formed with greater ease and electrophilic aromatic substitution is faster. Attack at the meta-position generates a cation that cannot transfer the charge to the ipso carbon and no +M effect is available. For substituents such as OR, therefore, ortho/para substitution should be faster than meta substitution, and bromination of anisole will give, primarily, 2-bromoanisole (443) and 4-bromoanisole (444) in roughly equal amounts.

Aromatic compounds that have substituents with a +I effect or a +I and a +M effect show an increase in the rate of electrophilic aromatic substitution relative to benzene and are said to be activating substituents.³⁴⁶ Since ortho and para products predominate with these activating groups, activators are also said to be ortho/para directors. A preference for either the ortho- or the para product is common, particularly in aromatic compounds that have several substituents. When 2-methylanisole was treated with bromine in chloroform, for example, a 94% yield of **445** was obtained as part of Vyvan Looper's synthesis of heliannuol D.³⁴⁷ Note that the presence of two activating groups allowed the reaction to proceed without adding a Lewis acid, which is typical.



Aromatic compounds that have substituents with a -*I* effect or a +*I* effect, and a +*M* effect show a decrease in the rate of electrophilic aromatic substitution, relative to benzene, and that substituent is said to be deactivating.³⁴⁶ This occurs when the substituent at the ipso carbon has a positive charge or a δ + dipole (SR₂, NO₂, CO₂R, SO₃R, NR₃, C=O or C=N). Reaction with the aromatic ring at the ortho or para position generates an intermediate that places a positive charge adjacent to the electrophilic center. An acetyl group is deactivating and the key

^{346.} Reference 327, pp 41-48, 51.

^{347.} Vyvyan, J.R.; Looper, R.E. Tetrahedron Lett. 2000, 41, 1151.

resonance structures for ortho, para and meta attack by X^+ are shown in 446, 447, and 448. In 446 and 447 a distinct –*I* effect is seen, as the positive charge of the intermediate resides on the ipso carbon, adjacent to the δ^+ dipole of the carbonyl. This interaction will destabilize these intermediates, making them more difficult to form in this rate-determining step and slowing the overall reaction. Attack in the meta position (see 448) cannot put the positive charge at the *ipso* carbon. The two electrophilic centers are relatively close together and this is destabilizing, but less destabilized than having the charges on adjacent atoms. Intermediate 448 is, therefore, *less destabilized* than 446 or 447 and will lead to the major product in this particular reaction, meta-substitution. Groups such as acetyl, nitro, and so on are deactivating and meta-directors. This analysis leads to the correct observation that nitration of nitrobenzene gives primarily 1,3-dinitrobenzene. Analysis of benzene derivatives that contain many types of substituents led to Table 2.15,³⁴⁸ which shows activating and deactivating groups, classified by their I and M effects. The table also shows if the substituent is an ortho/para or a meta director.



Halogenated benzenes show a deactivating effect similar to that for the deactivating groups listed, but give primarily ortho and para substitution products as in the formation of 1,2-dichlorobenzene and 1,4-dichlorobenzene from the reaction of chlorobenzene with Cl_2 and $AlCl_3$. This is explained by the fact that chlorine has a -I effect (making it deactivating) but a +*M* effect, making it an ortho/para director. This mesomeric effect is seen in **449** for para substitution. When the *I* and *M* effects are in conflict, as in chlorobenzene, the reaction is generally slower than if a pure +*I* and/or +*M* effect is possible.³⁴⁶

 Table 2.15.
 Substituent Effects in Electrophilic Aromatic Substitution

Substituent Type	Effect	Directing Effect	Example			
+ <i>I</i> , + <i>M</i>	Activating	ortho/para	alkyl groups, O [–]			
+ <i>I</i> , – <i>M</i>	Activating	ortho/para	SiMe ₃ , CO ₂ ⁻			
- <i>I</i> , + <i>M</i>	Activating	ortho/para	NMe ₂ , NHCO ₂ Me, OMe, Ph			
- <i>I</i> , + <i>M</i>	Deactivting	ortho/para	Cl, Br, CH=CHNO ₂			
-1	Deactivting	meta	Me_3N^+			
- <i>I</i> , - <i>M</i>	Deactivting	meta	NO ₂ , C≡N, COR			
[Reprinted with permission from Taylor, R. <i>Electrophilic Aromatic Substitution</i> , Wiley, Chichester, 1990 , p 51. Copyright © 1990 by John Wiley and Sons, Inc.]						

^{348.} Reference 327, p 51.

MOLECULAR MODELING: Local Ionization Potential Maps and Electrophilic Reactivity/ Selectivity

The degree to which substituents affect the electron distribution of a benzene ring to which they are attached may be accessed by a **local ionization potential map**. This colors an electron density surface that indicates overall molecular size and shape (where a reagent can approach), with the value of the energy required to expel an electron from a specific location on the surface. By convention, regions where the local ionization potential is large (electron ejection is difficult) are colored "blue", while regions where it is small are colored "red". Thus, it is possible to differentiate regions on the accessible surface that are best able to attack (donate electrons) to an electrophilic center (colored red) from those that are less likely to donate electrons and more likely to be attacked (accept electron density) in a reaction (colored blue).

Examine local ionization maps for benzene (acting as the standard), styrene, acetophenone, anisole, chlorobenzene and trimethylsilylbenzene (top left to right and bottom left to right). *SpartanModel* cannot calculate local ionization potential maps and these results were obtained using *Spartan*. The maps are initially presented as transparent models to allow you to see the underlying structures. Change to solid models to allow easier comparison. *Click* on one of the maps and select *Solid* from the *Style* menu at the bottom of the screen. Which substituents lower the local ionization potential (on the benzene ring) and hence would be expected to lead to an increase in electrophilic reactivity? For these substituents, is reaction at the *ortho* and *para* positions favored or disfavored over reaction at the *meta* positions? Which substituents, is reaction at the *ortho* and *para* positions at the *ortho* positions favored or disfavored over reaction favored or disfavored over reaction at the *meta* positions? Are the effects at the *ortho* positions smaller, larger, or about the same as at the *para* position? Are the conclusions from the local ionization potential maps consistent with arguments based on "resonance theory"? Elaborate.

Other factors influence the rate of electrophilic aromatic substitution, including steric hindrance and strain.³⁴⁹ When a substituent (X in **450**) is physically large, ortho substitution is inhibited by steric hindrance in the transition state which, in principle, makes it more difficult for that intermediate to form. This effect is observed when X is an alkyl group (see Friedel-Crafts alkylation, sec. 12.4.B). Many of the groups encountered in this section have heteroatoms, and the steric effect is often less important if the X group can coordinate with the incoming group. This type of coordination (or chelation) effect is represented in **451** and the result is an increase in the amount of the ortho product. With the heteroatom substituents discussed in this section, this model is more important, and the increase in ortho products at the expense of para products is called the **ortho effect**. Steric hindrance does play a significant role in substituents makes approach along path *c* sterically difficult. Paths *a* and *b* are accessible so substituents **452** will lead to products resulting from attack along paths *a* and *b*.

^{349.} Reference 327, p 52.



Deformation of an aromatic ring out of planarity leads to strain. 4,5-Dimethylphenanthrene (**453**) is an example, where the two methyl groups interact and the net result of this interaction is that the molecule is more reactive.³⁵⁰ Strain also occurs in molecules such as β -hydroxyindane (**454**), which is brominated at the γ -position to give **455**.³⁵⁰ The strain imparted by the five-membered ring makes the α -position less susceptible to electrophilic aromatic substitution. Formation of resonance intermediate **456** demands a shortened bond for the sp² hybridized carbon, and this increases the strain at that position. When this reaction occurs in a sixmembered ring such as β -hydroxytetralin (**457**), however, the strain in the intermediate is greatly diminished and bromination gives primarily the α -product, **458**. The explanation for this selectivity is known as the **Mills-Nixon effect**.³⁵¹



All of these effects are observed when comparing the rates of various electrophilic aromatic substitution reactions. Activating substituents increase the rate of reaction relative to benzene. The rate of reaction for the nitration of anisole, for example, was 9.7 x 10⁶ times faster than nitration of benzene. The reaction of anisole with nitric and sulfuric acids, gave 44% of *o*-nitroanisole, 56% of *p*-nitroanisole and < 1% of *m*-nitro-anisole.³⁵² This contrasts with reactions involving deactivating substituents, where selectivity for the meta product is usually very good. Nitration of nitrobenzene, for example, gave 1,3-dinitrobenzene in 94% yield, with only 6% of the ortho product and < 1% of the para product.³⁵²

^{350.} Reference 327, p 53.

^{351.} Mills, W.H.; Nixon, I.G. J. Chem. Soc. 1930, 2510.

^{352.} Reference 325, p 43.



Nitration of aromatic rings has been reported in ionic liquids such as $[bmpy][N(Tf)_2]$ (**459**).³⁵³ In this variation, an acyl nitrate formed from HNO₃-Ac₂O reacts with toluene to give a 93% yield of *ortho-* and *para*-nitrotoluene (o/p = 1.3) at room temperature in dichloromethane, in one hour

2.12.C. Nucleophilic Aromatic Substitution

An aromatic ring is electron rich and nucleophilic attack on that ring is expected to be difficult under normal reaction conditions. Nucleophilic aromatic substitution³⁵⁴ does occur, however, and is synthetically useful with a variety of substituents and nucleophiles. A variation of this aromatic substitution involves the reaction of aryl halides with cuprous salts, but this will be discussed in sec. 8.2.C. When dinitrochlorobenzene was treated with sodium hydroxide in aqueous media, or neat, no reaction occurred. When that mixture was heated to $\sim 100^{\circ}$ C, however, a substitution reaction occurred that converted 2,4-dinitrochlorobenzene into 2,4-dinitrophenol.³⁵⁵ Indeed, this is a commercial method for the production of phenol derivatives, despite the harsh reaction conditions. Direct substitution must occur by attack of the nucleophilic hydroxide at the *ipso* carbon, generating the resonance stabilized carbanion intermediate 460. The chloride is a leaving group, expelled by the negative charge (two electrons) in 460 and assisted by rearomatization of the ring to give the phenol derivative. The rate-determining step is the initial collision to form 460, and factors that make this collision more favorable will increase the rate of the overall substitution process. The I and M effects noted with electrophilic aromatic substitution are operative, but their effect will be the exact opposite for nucleophilic attack on 460 since the charges are different. An electron withdrawing group at the ortho or para positions relatively to the Cl, for example, will delocalize the negative charge and stabilize that intermediate. Conversely, an electron-releasing group at those positions will destabilize



the intermediate. Inspection of resonance contributor **461**, which arises by nucleophilic attack of hydroxide on 4-chloroanisole, shows the negative charge on the carbon adjacent to the OMe moiety. The electron rich oxygen will repel the negative charge and destabilize **461**, making nucleophilic substitution of 4-chloroanisole more difficult than for chlorobenzene. Resonance

^{353.} Lancaster, N.L.; Llopis-Mestre, V. Chem. Commun. 2003, 2812.

^{354.} Rossi, R.A.; de Rossi, R.H. *Aromatic Substitution by the SRN1 Mechanism*, American Chemical Society, Washington, DC, *1983*.

^{355.} Reference 325, p 134.

contributor **462**, arising from reaction of 4-chloronitrobenzene and hydroxide, has a negative charge on the carbon adjacent to the positive nitrogen of the nitro group. The charge can be delocalized out of the ring and onto the nitro oxygen, leading to an additional resonance structure and a more stable intermediate. Therefore, 4-chloronitrobezene should react faster than chlorobenzene. Stabilization of the anionic intermediate by a nitro group will be most effective at the ortho and para positions and much less effective when the substituents are in the meta position, all relative to the *ipso* carbon.



 Table 2.16. Influence of Substituents on Nucleophilic Aromatic Substitution.

$\begin{array}{c} \begin{array}{c} & & \\ $	N-H Y 464	N^+ NO ₂ Y Y 4	$\begin{matrix} NO_2 & & \\ CI & & Y \\ 165 \end{matrix}$	NO ₂ H'N+ 466	
	Y	<i>k</i> / <i>k</i> _B for 463	<i>k/k</i> _B for 465		
	NO_2	41000			
	CN	6000	5		
	CO ₂ Et	920	5		
	Br	10	35		
	Cl	6	32		
	OMe	0.025	4		
	Н	1	1		
	Me	0.2	0.9		
[Leon M. Stock, AROMATIC SUBSTITUTION REACTIONS, ©1968, pp. 87. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey.					

For nucleophilic aromatic substitution, electron-withdrawing groups stabilize the reactive intermediates and enhance the rate of the reaction. These effects are shown in Table 2.16,³⁵⁶ which compares the relative rates of nucleophilic substitution of chlorobenzene derivatives with piperidine. Electron-donating substituents destabilize the reactive intermediate and diminish the rate of the reaction, which is dramatically illustrated by the reaction of 2,4,6-trinitrochlorobenzene with dilute hydroxide, which gave trinitrophenol upon simple warming and did not require high temperatures or pressures. In Table 2.16, rate enhancement is greatest when the substituent (Y) is in the para position, although some rate enhancement is observed for the meta substituent as well. Compounds with a para substituent in **463**, relative to the chlorine leaving group, stabilized the intermediate that led to formation of **464**, and there was a large rate effect for all electron withdrawing substituents. The derivative with a meta

^{356.} Reference 325, p 87.

substituent relative to the chlorine leaving group (465), generated 466 and showed a smaller rate effect. Electron withdrawing groups exerted the largest influence (the reference compound was $Y = H [k_H = 1]$ in all cases.

2.12.D. Benzyne Derivatives

When aryl halides are treated with powerful bases such as potassium amide (KNH₂) or *tert*butyllithium (sec. 8.5.B), a hydrogen atom may be removed from the aromatic ring in an acidbase reaction to give an aryl carbanion. The presence of the halogen in aromatic compounds such as **467** makes the ortho hydrogens more acidic. Removal of the ortho hydrogen generates a carbanion (**468**), but the negative charge is generated perpendicular to the plane of the aromatic π -cloud (see **468B**). The charge resides on the carbon next to the halogen, which is a good leaving group. Elimination of the halide forms a new π bond that is perpendicular to the π -cloud of the benzene ring in a highly reactive species (**469** and see **409**) called a benzyne.



In a specific example, **467** was treated with sodium amide and deprotonation gave **468A**, from which the bromide was expelled to give the benzyne intermediate, **469A**.³⁵⁷ When **468A** is redrawn as **468B**, it is clear that the carbanionic center is perpendicular to the aromatic π cloud and parallel to the C-Br bond. Expulsion of this adjacent leaving group forms the new π bond of the benzyne intermediate (**468B** \rightarrow **469B**). This π -bond is subject to nucleophilic attack, and the LUMO map (see sec. 2.9.A) shown for **469B** indicates a blue color for the two

 ⁽a) Roberts, J.D.; Simmons, Jr., H.E.; Carlsmith, L.A.; Vaughn, C.W. J. Am. Chem. Soc. 1953, 75, 3290; (b) Roberts, J.D.; Semenow, D.A.; Simmons, Jr., H.E.; Carlsmith, L.A. Ibid 1956, 78, 601; (c) Roberts, J.D.; Vaughn, C.W.; Carlsmith, L.A.; Semenow, D.A. Ibid 1956, 78, 611.

benzyne carbon atoms (see **Spartan file C2-469B** under the **Chapter 2 directory**), suggesting that they are susceptible to attack by a nucleophile. The more intense blue at C3 relative to the methoxy group suggests that the 3-amino product will predominate. Indeed, the nucleophilic amide reacts with **469** to produce a mixture of carbanions **470** and **473**, the result of attack at both carbons of the double bond. Subsequent reaction with water generates the neutral aniline derivatives **471** and **472**. One substitution product (**473**) has the new amino substituent adjacent to the carbon that bore the bromide leaving group, and this product is said to result from **cine substitution**.

Benzyne formation and their reactions are not limited to simple benzene derivatives. Heterocyclic molecules can also be used for benzene reactions. One important use of benzyne derivatives is in the Diels-Alder reaction (see sec. 11.4.A). When 3-chloro-2-methoxypyridine (474) was treated with LDA at -78°C, for example, lithium-hydrogen exchange occurred to give 475. Loss of LiBr led to benzyne 476, which reacted with furan to give the Diels-Alder product (477) in 74% yield.³⁵⁸



2.12.E. Substitution Reactions of Aryl Diazonium Salts

When a primary aromatic amine such as aniline is treated with nitrous acid (HONO), usually generated by the reaction of sodium nitrite and HCl or $H_2SO_{4,}^{359}$ an aryl diazonium compound is formed, in this case benzenediazonium chloride (**478**).³⁶⁰ The nitrogen fragment of a diazonium ion (Ar–N₂⁺) is one of the best leaving groups known^{360a,b} and it can be displaced by a variety of nucleophiles to give the substitution product (**479**).³⁶¹

Many different nucleophiles can react with aryl diazonium salts, often by different mechanisms that range from S_N1 type processes to those involving radicals.³⁶² Heating **478** in aqueous acid generates phenol.³⁶³ This reaction is also illustrated by the conversion of 3-nitroaniline (**480**)

358. Connon, S.J.; Hegarty, A.F. J. Chem. Soc. Perkin Trans. 1 2000, 1245.

- 362. Wulfman, D.S. in *The Chemistry of Diazonium and Diazo Groups, Part 1*, Patai, S. (Ed.), Wiley, New York, **1978**, pp 286-297.
- 363. Horning, D.E.; Ross, D.A.; Muchowski, J.M. Can. J. Chem. 1973, 51, 2347.

^{359. (}a) Ridd, J.H. Quart. Rev. Chem. Soc. 1961, 15, 418; (b) Hegarty, A.F. The Chemistry of Diazonium and Diazo Groups, Part 2, Patai, S. (Ed.), Wiley, New York, 1978, pp 511-591.

^{360. (}a) Collins, C.J. Acc. Chem. Res. 1971, 4, 315; (b) Friedman, L. in Carbonium Ions, Vol. II, Olah, G A.; Schleyer, P.v.R. (Eds.), Wiley, New York, 1970, p 655; (c) Wistar, R.; BartLett. P.D. J. Am. Chem. Soc. 1941, 63, 413.

^{361.} Reference 325, pp 92-100.

to the diazonium salt (481), which was followed by heating in aqueous sulfuric acid to give 3-nitrophenol (482).³⁶⁴



Treatment of diazonium salts with cuprous, Cu(I), salts generates aryl halides. When **478** reacts with CuCl (cuprous chloride) or CuBr (cuprous bromide), the products are chlorobenzene or bromobenzene via what is probably a radical reaction.³⁶⁵ This conversion is known as the **Sandmeyer reaction**.³⁶⁶ The use of copper powder rather than cuprous salts for this transformation is often called the **Gattermann reaction**.^{367,366b,c} Aryl iodides are also produced from diazonium salts by reaction with potassium iodide (KI), but the actual reactive species may be $I_3^{-.368,369}$ In a synthesis of dichroanal B, Banerjee and co-workers treated aniline **483** with sodium nitrite in aqueous HBr to form the diazonium salt, and subsequent heating with CuBr gave an 88% yield of aryl bromide **484**.³⁷⁰ Aryl nitriles are generated under Sandmeyer conditions using cuprous cyanide (CuCN), as in the conversion of **485** to benzonitrile derivative **487**, via diazonium chloride **486**.



- 364. Reference 325, p 95.
- 365. (a) Dickerman, S.C.; DeSouza, D.J.; Jacobson, N. J. Org. Chem. 1969, 34, 710; (b) Kochi, J.K. J. Am. Chem. Soc. 1957, 79, 2942.
- 366. (a) Sandmeyer, T. *Berichte* 1884, 17, 1633, 2650; (b) Mowry, D.T. *Chem. Rev.* 1948, 42, 189 (see p 213);
 (c) Hodgson, H.H. *Ibid* 1947, 40, 251; (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-83; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd Ed.* Wiley-Interscience, New Jersey, 2005, pp. 288-289.
- 367. Gatterman, L. Berichte 1890, 23, 1218.
- 368. Carey, J.G.; Millar, I.T. Chem. Ind. (London) 1960, 97.
- 369. Reference 325, p 96.
- 370. Banerjee, M.; Mukhopadhyay, R.; Achari, B.; Banerjee, A.Kr. Org. Lett. 2003, 5, 3931.



Nitrogen can be completely removed from a diazonium salt by reduction with H₃PO₂ (hypophosphorus acid).³⁷¹ This technique is often used in conjunction with using the electron withdrawing properties of a nitro group to position another group. Reduction to an amine, diazotization and then reduction resulted in loss of nitrogen and removal of nitrogen from the molecule. The amine moiety itself can be used to position groups, and this is very useful since the amine unit is electron releasing. Diazotization and reduction removes nitrogen as before. The deamination process is illustrated by the conversion of aryl diamine **488** to the bis(diazonium) salt **489**, and subsequent reduction to the biaryl **490**.³⁷² In basic solutions, of an activated aromatic substrate, diazonium salts decompose and couple to give biaryls (Ar–Ar).³⁷³ Reaction of benzenediazonium ion (**385**) and toluene gave a 67% yield of **491**, along with 19% of **492** and 14% of **493**.³⁷³ This result suggests the coupling is rather unselective. Selectivity is observed only when the substituent is part of the aryl diazonium ion, as in the conversion of **494** to **495**.³⁷³



2.13. CONCLUSION

This chapter has attempted to show that a few reaction types dominate much of the chemistry used by organic chemists on a daily basis. It is also meant as a review of the fundamental functional group transformations encountered in a typical undergraduate organic chemistry course. Chapters 3 and 4 will discuss the place of oxidation and reduction reactions in organic chemical transformations, which will be followed by hydroboration in Chapter 5 and then a discussion of protecting groups in chapter seven. Chapter 6 will discuss methods for

^{371.} Kornblum, N. Org. React. 1944, 2, 262.

^{372.} Reference 325, p 97.

^{373.} Reference 325, p 99.

controlling stereochemistry and regiochemistry and then macrocyclization reactions. Some of the important concepts in Chapter 6 will be introduced in Chapters 3-5, and Chapter 6 will attempt to tie those concepts together.

HOMEWORK

1. From the rate data given for compound **A** (in the table below), it is clear that the presence of a methoxy group significantly enhances the rate of solvolysis of **A**. Offer a reasonable mechanistic explanation of this solvolysis reaction that is consistent with the observed rate data.

Assume that differences in the rate due to changing the leaving group is insignificant for this question.



- 2. Reaction of 3-pentanol with potassium iodide in aqueous ethanol gave no reaction under several different reaction conditions. If one adds a catalytic amount of *para*-toluenesulfonic acid, however, the reaction proceeds to give 3-iodopentane. Explain these observations.
- 3. Explain why the obvious $S_N 2$ conditions shown in the following reaction give only elimination and no substitution with this secondary bromide.



4. Explain each of the following trends.

(a) Order of basicity.
$$O_2N - O_Na^+ < O_Na^+ < MeO - O_Na^+ < O_Na^+ < O_Na^+$$

(b) Order of acidity. $HCO_2H > CH_3CO_2H > O_MB > OH CH_3CO_2H$ in water > CH_3CO_2H in THF

5. Give the major product for each of the following transformations involving conversion of a carboxylic acid or a derivative into another acid derivative.



6. Explain why the ¹⁴C label is found at both C1 and C2 in the aniline product despite the fact that the label is localized on C1 in the chlorobenzene precursor. The * indicates the position of the ¹⁴C label.

7. Does the bromide shown below undergo an E2 reaction? If so, draw the major product(s). If not, why not?



8. Offer a mechanistic explanation for the following transformation.



9. The following reaction gives a mixture of the alcohol and the ether, in the proportions given later in this question. Only 0.03 eq of 1-octene were used. In each case, a 1:1 ratio of water to alcohol was used.

$$C_{6}H_{17}CH=CH_{2} \xrightarrow[]{1. Hg(OAc)_{2}, H_{2}O/ROH} Sodium dodecyl sulfate} C_{6}H_{17}CHCH_{3} + C_{6}H_{17}CHCH_{3}$$

Reaction with 1.0 equivalent of 1-octanol (to 0.03 eq of 1-octene) gave a 98:2 mixture of alcohol/ether in 50% aq THF. The use of 10 equivalents of 1-octanol in 0.3 M THF in water gave a 52:48 mixture of alcohol/ether. Explain what the 52:48 mixture tells you about the relative nucleophilicity of water and 1-octanol. Explain why increasing the amount of 1-octanol leads to more ether product.

10. Two products are formed in the following reaction, A and B. (a) Offer a reasonable explanation of how B could arise in this reaction. (b) Would the use of the 4-chlorophenyl derivative, rather than the 4-methoxy derivative help or hurt formation of B? Why or why not?



11. Offer a mechanistic explanation for the following transformation.



12. Treatment of alcohol A leads to B in 70% yield. Explain this product in terms of a mechanism and comment on why the C=C unit is generated between C2-C3 rather than between C2-C1 [hint, see sec. 6.3.B].



13. Suggest a mechanism for the following transformation.



14. Suggest a reasonable mechanism for this reaction.



- 15. Explain each of the following.
 - (a) Heating 2-*N*,*N*,*N*-triethylammonium)butane gives ethene rather than 1-butene.
 - (b) The reaction of the epoxide shown gives the $S_N 2'$ product rather than the $S_N 2$ product. Draw the $S_N 2'$ product, and explain why it is formed preferentially.

$$F \xrightarrow{O} Ph \xrightarrow{2 \text{ eq BuLi, THF}} 0^{\circ}C, 2 h$$

(c) This reaction is *faster* in aqueous ethanol than in 100% ethanol:

$$\sim$$
 I $\xrightarrow{\text{NEt}_3}$ $\xrightarrow{\text{NEt}_3}$ I

- (d) $H_3N^+CH_2CO_2H$ is a stronger acid than $H_3N^+(CH_2)_4CO_2H$.
- (e) $O_2N \longrightarrow OH$ is a stronger acid than $\bigcirc OH$
- 16. 3-Bromo-4-methylhexane is drawn in two different orientations, A and B. Using an E2 reaction, remove H_a and convince yourself that the two orientations lead to the same alkene. Explain this observation, and why an E2 reaction leads to one alkene but an E1 reaction leads to a mixture of (*E*) and (*Z*) isomers.



17. Offer a mechanistic explanation for the following transformation.



18. Offer a mechanistic explanation for the following transformation.



19. Offer a mechanistic explanation for the following transformation.



20. For each of the following give the major product, with all appropriate stereochemistry. If there is no reaction, indicate by N.R.





21. For the reaction shown, (a) Draw the transition state (b) Give the major product (c) What type of reaction is this?

$$\underset{H}{\overset{\text{H}}{\underset{\text{Br}}}} \underset{Br}{\overset{\text{Et}}{\underset{\text{H}}}} \underset{Ph}{\overset{\text{ROH}, \text{EtOH}}{\underset{\text{EtOH}}}}$$

22. In each case, predict the major product and explain your answer.



 For the following reaction, predict the product and show the correct stereochemistry. Use Newman projections to indicate how you chose your product and to justify your answer.



24. For each of the following, show the major product. Explain your choice.



25. For each of the following provide a suitable synthesis. Show all intermediate products and all reagents.



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chapter 3 Oxidation

3.1. INTRODUCTION

Oxidation in organic chemistry has historically been defined in terms of reactivity. A broad definition by Sheldon and Kochi states "oxidation in Organic chemistry refers to either (1) the elimination of hydrogens, as in the sequential dehydrogenation of ethane, or (2) the replacement of a hydrogen atom bonded to carbon with another more electronegative element such as oxygen in the following series of oxidative transformations of methane:"¹

 $CH_4 \longrightarrow CH_3OH \longrightarrow CH_2O \longrightarrow HCO_2H \longrightarrow CO_2$

Oxidation can also be defined as reaction of an element with oxygen,² analogous to the second criterion stated above. A more general definition, applied most often in inorganic chemistry, involves the loss of one or more electrons from an atom or group.² Soloveichik and Krakauer³ listed five criteria that could be used to identify an oxidation process for a given organic reaction, and arrange compounds by their ability to be oxidized.

- 1. Pauling's electronegativity scale.⁴
- 2. The oxidation number of the parent substance of each homologous series under consideration.
- 3. The ratio of bond moment to bond length, μ/l (net charge).⁵
- 4. Hammett's sigma function as revised by Taft (Taft's σ^*).⁶
- 5. Chemical reactions of the substance involved, particularly hydrolysis, which does not provide fundamental changes in oxidation stage if certain conventions are maintained.³

^{1.} Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds,* Academic Press, New York, *1981*, p 6.

^{2.} Yalman, R.G. J. Chem. Educ. 1959, 36, 215.

^{3.} Soloveichik, S.; Krakauer, H. J. Chem. Educ., 1966, 43, 532.

^{4.} Pauling, L. Nature of the Chemical Bond, 3rd ed., Cornell U. Press., Ithaca, New York, 1940, pp 221-231.

^{5. (}a) Del Re, G. *Electronic Aspects of Biochemistry*, Pullman, B. (Ed.), Academic Press, New York, **1964**, pp 221-231; (b) Smyth, C.P. *Dielectric Behavior and Structure*, McGraw-Hill, New York, **1955**, pp 244-245, 247.

 ⁽a) Taft, Jr., R.W. J. Am. Chem. Soc. 1952, 74, 2729; (b) Taft, Jr., R.W. Ibid. 1958, 75,4231; (c) Taft, Jr., R.W. Steric Effects in Organic Chemistry, Chapter 13, Newman, M.S. (Ed.), Wiley, New York, 1956, pp 556-675.

These criteria allow the oxidation state of a molecule to be determined, which is useful for categorizing a reaction as an oxidation or a reduction. Soloverchik and Krakauer listed another set of rules for determining the oxidation state of a molecule:³

- 1. The oxidation state of carbon in hydrocarbons of the methane series is zero
- 2. The oxidation state is increased by one for each bond with a hydrogen atom or an alkyl group replaced by a bond with a more strongly electron attracting atom or group (-NH₂, SH, halogen, CO₂, etc.) for every removal of a pair of hydrogen atoms from two adjacent carbon atoms.
- 3. The group on a carbon is defined by its substituent carbons bearing the same substituents belonging to the same group. Groups within an oxidation state are arranged in order of increasing induced electron deficiency of the function bearing carbon. (CH₃X > RCH₂X > R₂CHX > R₃CX).

With these rules, one can determine if a starting material and a product are in a higher or a lower oxidation state. There are several structural types, and an oxidation is defined as conversion of a group from a lower stage to a higher stage (I \rightarrow II, II \rightarrow III, etc.).³ Examples are R₃CNH₂ \rightarrow R₂C=NH (I \rightarrow II); RCONH₂ \rightarrow (H₂N)₂C=O (III \rightarrow IV); and, AcCR₃ \rightarrow R₂C=O \rightarrow RCl₃ \rightarrow Cl₃CCO₂H (I \rightarrow II \rightarrow III \rightarrow IV).³

A loss of electrons is associated with the change in oxidation state of an atom, and electron loss can be determined by a device known as **oxidation number**. Holleran and Jespersen⁷ listed several rules to determine the oxidation number or each atom within a molecule. The change in the numbers between starting material and products shows the loss or gain of electrons and the change in oxidation state.

- 1. The sum of the oxidation numbers of all the atoms in a molecule or ion must equal the total charge (0 for a neutral molecule).
- 2. Metallic atoms of groups 1 and 2 have oxidation numbers of +1 and +2, respectively.
- **3.** H and F are assigned oxidation numbers of +1 and -1, respectively, when part of a molecule.
- 4. Oxygen is assigned an oxidation number of -2 in its compounds except for peroxide, where it is -1, and for OF₂, where it is +2.
- 5. Atoms of group 7 are assigned oxidation numbers of -1 in their binary compounds.
- 6. In binary compounds, atoms from groups 16 and 15 are assigned oxidation numbers of -2 and -3, respectively.
- 7. If two rules conflict, the rule that occurs first takes precedence.
- 8. If a conflict occurs within the same group, the lighter element takes the charge (I is +1

^{7.} Holleran, E.M.; Jespersen, N.D. J. Chem. Educ. 1980, 57, 670.

in ICl).

Oxidation numbers can be assigned to any atom, as shown in the following examples:

 H_2O_2 (1 for O) BrO_3 (+5 for Br) OF_2 (+2 for O) LiO_2 (-12 for O)

If an element is not included explicitly in one of the rules its oxidation number is found by difference, as in the case of the nitrite ion. The symbol Σ below refers to the net charge for the molecule, as determined by the usual formal charge calculations. For the N in NO₂⁻, NO₂⁻ (each O = -2, Σ = -1, therefore, N = +5).

A simplified version of this approach was used by Hendrickson, Cram and Hammond⁸ and later by Pine⁹ in their undergraduate organic textbooks. The rules shown above were applied only to those atoms most commonly encountered in simple organic molecules: H, O, C, N, and the halogens. Hendrickson, Cram, Hammond and Pine used the following convention for assigning oxidation numbers.^{8,9}

- -1 for hydrogen
- 0 for carbon (bonds to same atom)
- +1 for a covalent bond to a heteroatom (usually oxygen or halogen)

The oxidation number should be determined only for those atoms that are modified or changed as a result of the reaction. If the sums of the oxidation numbers of the various atoms in the starting material and in the product are compared, the change in oxidation number will indicate an oxidation or a reduction.

An example is the oxidation of 1-propanol to propanal, which is subsequently oxidized to propanoic acid in a second step. In 1-propanol, the carbon bearing the hydroxyl group has an oxidation number of -1 (C is 0, each H is -1, and O is +1). The oxidation number of carbon in propanal is +1 (C is 0, H is -1, O is +1, and O, from the second bond to the carbonyl, is +1). The change in oxidation number is $-1 \rightarrow +1$, for a net **loss** of two electrons, and an oxidation. Remember that as the net charge becomes more positive, this is associated with loss of electrons, which have a negative charge. Similarly, the carbon of interest in propanoic acid has an oxidation number of +3 (C is 0, the three bonds to oxygen total +3). Conversion of propanal to propanoic acid involves the *loss* of two additional electrons ($+1 \rightarrow +3$), and is an oxidation. Each of these two electron oxidations is a one-stage oxidation, but a direct conversion of 1-propanol to propanoic acid would be a four electron, two-stage oxidation. Only the carbon bearing the oxygen atoms was examined in this example since the other carbons are not changed during the course of the reaction.

^{8.} Hendrickson, J.B.; Cram, D.J.; Hammond, G.S. Organic Chemistry, 3rd Ed., McGraw-Hill, New York, 1970.

^{9.} Pine, S.H. Organic Chemistry, 5th Ed., McGraw-Hill, New York, 1987.



The oxidation of 2-butene to the corresponding epoxide (sec. 3.4) involves modification of two carbons. The oxidation number of each carbon comprising the π bond is -1 (C,C is 0, and H is -1), and the oxidation number of each epoxy carbon in the product is 0 (C,C is 0, O is +1 and H is -1), for a change of one electron ($-1 \rightarrow 0$) for *each* of those two carbons. The *net* change for each molecule is loss of two electrons for a one-stage oxidation.

If there is a choice of more than one reagent for a particular oxidation reaction, the relative strength of those reagents is important. It is also important to determine whether a given reagent will induce a one or two-stage (two electron or four electron) oxidation (1-propanol to propanal or 1-propanol to propanoic acid, for example). Oxidation and reduction are linked together, since an oxidation of one species is accompanied by reduction of another. A useful measure of the propensity of a compound or a reagent for oxidation-reduction is the reduction potential. The reduction potential is obtained from polarographic (electrolysis) experiments that involve transfer of electrons between electrodes.¹⁰ "An electrode process is a heterogeneous transfer of electrons between electrodes and an organic molecule".¹¹ The potential of the electrode controls the availability of electrons in the medium. The tendency toward electron loss or electron gain in the reduction system is given by the reaction

M \longrightarrow M²⁺ + 2 e⁻

Reduction potential can be measured as an electrical driving force, expressed as the electrode potential.¹¹ As written, this equation represents a loss of two electrons from M and is an oxidation. If written as the reverse reaction, it is a reduction. Both oxidized and reduced species must be present in this equilibrium, and changes in potential occur as the equilibrium shifts. It is important to note that the electron transfer process shown above does not always correlate with the functional group transformation associated with oxidation of organic substrates. It does allow comparisons of the relative strengths of various oxidizing agents, however. For selected reactions involving electrochemistry of organic substrates see section 4.9.J.

If the electrode potential in an electrolysis reaction is made more positive, oxidation (with loss of electrons) will compensate for this positive change in potential.¹² A more negative potential will be compensated for by addition of electrons to the oxidized form. The equilibrium potential of a reversible system of this type can, therefore, be given by the equation

^{10.} Ross, S.D.; Finkelstein, M.; Rudd, E.J. Anodic Oxidations, Academic Press, New York, 1975.

^{11.} Reference 10, p 7.

^{12.} Allen, M.J. Organic Electrode Processes, Reinhold Pub. Corp. New York, 1958, pp 2.

$$E = E_o - \frac{RT}{nF} \ln \frac{[Ox]}{[Red]}$$
 3.1

where E_0 is the standard reduction potential and F is **Faraday's constant** (96,400 Coulombs per equivalent). Ox and Red refer to the oxidized and reduced forms, respectively. Electrode potential is always expressed relative to an arbitrary standard, and the zero electrode potential is usually taken as that of "the reversible equilibrium between hydrogen gas at one standard atmosphere pressure and hydrogen ions at unit activity" (the normal reversible hydrogen electrode potential).¹³ For the reaction,

M \longrightarrow M^{2+} + e^-

the metal (M) is assumed to be coupled with a metal having less tendency to ionize, generating a negative potential in the electrolytic cell. The electrode potential (ϵ) is proportional to the free energy (ΔG) of the reaction by

$$\Delta G = -z \,\mathrm{F} \,E \,\,\mathrm{for}\,\,\mathrm{the}\,\,\mathrm{cell} \tag{3.2}$$

$$\Delta G = -z F \varepsilon \text{ for a single electrode}$$
 3.3

where *E* is the electromotive force, F is the Faraday constant and *z* is the number of electrons involved in the overall cell reaction. If ε is negative, ΔG is positive and the reaction is *not* spontaneous. Using the **European convention**,^{14,15} ε° for a metal is taken as negative when the polarity of the metal in that cell is negative. Therefore, the expression $\Delta G = -[-z F \varepsilon]$ will be used for the reaction. An example is

Na \longrightarrow Na⁺ + e⁻

where ε^{o} is negative, ΔG is negative and ionization (a one-electron oxidation) is a spontaneous reaction.

The oxidation potential represents the ability of a metal atom (M) to be ionized to an ion (M^+) with loss of an electron. For the oxidation of organic molecules, transition metal compounds containing chromium, manganese, ruthenium, selenium, silver, or cerium are often used. The oxidation potential can be a useful method for examining the oxidizing power of these reagents.

Permanganate (MnO_4^-) is a powerful oxidizing agent used in many organic oxidations, but several other oxidation states areavailable to manganese, including manganate ($MnO_4^{2^-}$) and hypomanganate ($MnO_4^{3^-}$). Their reactivity toward reductants (the organic substrate) varies

^{13.} Reference 10, p 9.

^{14.} Reference 10, p 10.

^{15.} Ives, D.J.G.; Janz, G.J. Reference Electrodes: Theory and Practice, Academic Press, New York, 1961.

inversely with the charge on the oxidant, ^{16a} and the *relative order of oxidizing power* is

$$MnO_4^- > MnO_4^{2-} > MnO_4^{3-}$$
.

The reduction potentials for these species are known to be^{16a}

 $MnO_{4}^{-} + e^{-} \longrightarrow MnO_{4}^{2-} \qquad (\epsilon = +0.558 \text{ V})$ $MnO_{4}^{2-} + e^{-} \longrightarrow MnO_{4}^{3-} \qquad (\epsilon = +0.285 \text{ V})$

These reactions are shown as the standard reduction potential (see below) since reduction potential reflects the propensity of a metal or metal salt to be reduced, with concomitant oxidation of an organic substrate. The larger reduction potential for permanganate is correlated with its stronger oxidizing ability. The point of this example is that the oxidizing agents used in this chapter are not always metals but are often metal derivatives. Their oxidizing power varies with the structural features of each derivative, and it is important to understand the oxidizing power of each when they are used for the oxidation of an organic substrate. Oxidizing power varies with the reaction medium. Permanganate, for example, shows different reduction potentials in acidic and basic media:^{16a}

$$MnO_4^- + 3 e^- + 4 H^+ \longrightarrow MnO_2 + 2 H_2O \quad (\epsilon = +1.679 V)$$
$$MnO_4^- + 3 e^- + 2 H_2O \longrightarrow MnO_2 + 4 OH^- \quad (\epsilon = +0.59 V)$$

The standard reduction potential for many common metal salts and other compounds are known,¹⁷ and the pH of the media plays an important role in the oxidizing power of a given reagent. Acidic, neutral, and basic media will be employed in the following sections for the oxidation of different substrates and a variety of oxidizing agents will be used. The choice of reagent and conditions will influence the overall reaction, and determine if the oxidation is a two electron (one-stage) or a four-electron (two-stage) oxidation.

In most compilations of reduction potentials, the reaction is shown as the reduction potential $(M^+ + e^- \rightarrow M)$. The listed potential is also the oxidation potential for the reverse of the reaction shown. In general, the larger the reduction potential, the greater will be the oxidizing power of that reagent. Ozone, hydrogen peroxide, oxygen, lead [Pb(IV)], silver (Ag⁺), chromium [Cr(VI)], permanganate (MnO₄⁻), and periodic acid are strong oxidizing agents and will figure prominently in this chapter.

Reduction potential can also be correlated with ionization potential (I), which is defined by

 ⁽a) Stewart, R. in Oxidation in Organic Chemistry, Part A, Wiberg, K. (Ed.), Academic Press, New York, 1965, p 11; (b) Hudlicky', M. Oxidations in Organic Chemistry, American Chemical Society Monograph 186, Amer. Chem. Soc. Washington D.C., 1990.

^{17.} Handbook of Chemistry and Physics, 87th ed., CRC/Taylor and Francis, Boca Raton, Fla., 2006, pp 8-20-8-32.
$$M_{gas} \longrightarrow M^+ + e^- 3.4^{18}$$

The primary difference between I and the reduction potential (ε) is that I is defined for a gasphase reaction, whereas ε is measured in solution. The solvent has a great influence on the course of the oxidation. It is difficult to directly correlate ε and I, but the latter can be used for a general comparison of the ability of a molecule or reagent to be oxidized or reduced. In general, larger ionization potentials are correlated with greater oxidizing power. In Table 3.1, osmium tetroxide $(I = 12.97 \text{ eV})^{19}$ is a stronger oxidizing agent than ruthenium tetroxide $(I = 12.97 \text{ eV})^{19}$ 12.33 eV)¹⁹ by this criterion. It would be useful to know the reduction potentials of the organic substrates that are being oxidized, but these are difficult to obtain since the reduction potential will be different for each type of oxidation. For this reason, comparison of one-electron oxidations (the usual first half-wave potential reported for most organic molecules) can be misleading. The ionization potential is a useful alternative, but suffers from the same problem since it represents loss of one electron to form the ion. Table 3.1¹⁹ lists the ionization potential for common organic substrates that can be oxidized (many will be discussed in this chapter), as well as the ionization potential for a few selected oxidizing agents. There are different types of oxidations for the same substrate. Taking an alkene as an example, the reader is cautioned to remember that the ability of an alkene to be oxidized will depend on whether the reaction is an epoxidation, dihydroxylation, halogenation, or an oxidative cleavage. With that caution in mind, the data in Table 3.1 suggest that primary alcohols are more easily oxidized than secondary alcohols (the lower value of *I* represents a substrate that is more easily oxidized), and alkenes are more easily oxidized than alkynes. The ionization potentials also suggest that sulfides and tertiary amines are easily oxidized.

<u>Molecule</u>	<u>I (eV)</u>	Molecule	<u>I (eV)</u>	Molecule	<u>I (eV)</u>
MeC=CH	10.36	MeCO ₂ Me	10.27	MeCHO	10.20
benzene	9.24	Me-S-Me	8.68	EtCHO	9.98
NMe ₃	8.82	Cl ₂	11.48	acetone	9.69
O ₂	12.06	I ₂	9.28	cyclohexanone	9.14
H_2O_2	11.00	OsO_4	12.97	MeCOOH	10.36
EtOH	10.49	2-butene	9.13	PMe ₃	8.60
1-propanol	10.10	EtNH ₂	8.86	Et-S-Et	8.43
2-propanol	10.15	Et ₂ NH	8.01	Br ₂	10.54
phenol	8.51	O ₃	12.30	RuO ₄	12.33
[Reprinted with permission from <i>Handbook of Chemistry and Physics, 87th ed.,</i> CRC Taylor and Francis, Boca Raton, Fla., 2006 , pp 10-203-10-223. Copyright CRC Taylor & Francis, Boca Raton, FL.]					

Table 3.1.	Ionization	Potentials of	Common	Oxidizable	Organic	Substrates.

18. Reference 10, p 9.

19. Handbook of Chemistry and Physics, 87th ed., CRC/Taylor and Francis, Boca Raton, Fla., 2006, pp 10-203-10-223.

In the following sections, the emphasis will be on oxidation reactions that transform one functional group into another. Important transformations will be the oxidation of alcohols to carbonyls, oxidation of alkenes to diols or epoxides, and oxidative cleavage of alkenes to carbonyl derivatives. A few methods will be discussed for the oxidation of alkyl fragments, such as oxidation of a methyl group to hydroxymethyl, an aldehyde, or a carboxylic acid. The oxidation of sulfur and nitrogen compounds will also be briefly discussed. As mentioned, any attempt to classify organic reactions by the oxidizing power of the reagent is difficult since the classification depends on both reaction and reagent. Similarly, classification by organic substrate is difficult since there are oxidations involving transfers of different numbers of electrons, giving different products. The choice of classification by functional group transform is intended to convey a general sense of the use of oxidation in organic synthesis and is specifically correlated with the disconnection-transform theme of this book. The reader is referred to Hudlicky 'sexcellent monograph^{16b} for a thorough synthetic discussion of oxidation reactions.

3.2. ALCOHOLS TO CARBONYLS (CH-OH \rightarrow C=O)

One of the most important oxidations in organic chemistry converts alcohols to aldehydes, ketones, or carboxylic acid derivatives. Many oxidizing agents can be used, but the particular product formed depends on the structure of the alcohol as well as the reagent.²⁰ Primary alcohols are initially oxidized to aldehydes, which can be isolated, but that aldehyde can be oxidized further to a carboxylic acid. Each of these oxidations is a two-electron process. In many cases, the aldehyde is not isolated but converted directly to the carboxylic acid. Secondary alcohols can be oxidized to ketones via a two electron process, but oxidative cleavage (this would be a four-electron oxidation) can occur if the oxidation conditions are too harsh. The discussion of alcohol oxidation must focus on the relative strength of the reagent, the conditions under which it is used, and structural variations of the alcohol substrate. This section will begin with the most common alcohol oxidizing reagents, which are based on Cr(VI). A discussion of other reagents, including the use of DMSO reagents, the Dess-Martin periodinane reagent (sec. 3.D), tetrapropylammonium perruthenate (TPAP, $Pr_4N^+RuO_4^-$), and others will follow.

3.2.A. Oxidation with Chromium (VI)

Chromium (VI) is a strong oxidizing agent. In sulfuric acid, the reaction of Cr(VI) has a reduction potential of 1.10 V,¹⁷ but several chromium species may be present:

$$Cr^{6+} + 3e^- \rightarrow Cr^{3+}$$
 (2N H₂SO₄) 1.10 V

$$Cr_2O_7^{2^-} + 14 H^+ + 6 e^- \rightarrow 2 Cr^{3^+} + 7 H_2O$$
 1.33 V

^{20.} Larock, R.C. Comprehensive Organic Transformations, 2nd ed., Wiley-VCH, New York, 1999, pp 1234-1256

$$HCrO_4^- + 7 H^+ + 3 e^- \rightarrow Cr^{3+} + 4 H_2O$$
 1.195 V

3.2.A.i. Chromium Reagents. Oxidation of an alcohol is accompanied by reduction of the chromium [Cr (VI) \rightarrow Cr(III)]. As implied by the reduction potentials of the three chromium species shown, there are many Cr(VI) reagents.^{21,22} The inorganic reagent chromium trioxide is commonly used, which is a polymeric species usually written as (CrO₃)_n. In aqueous media, chromium trioxide exists in equilibrium with several other Cr(VI) species, including H₂CrO₄, HCrO₄⁻, CrO₄²⁻, HCr₂O₇, Cr₂O₇²⁻, H₂Cr₂O₇, and HCr₂O₇⁻²³ Of the Cr(VI) species listed above, dichromate is the strongest. Oxidation of alcohols requires that both the alcohol and the chromium oxidant are soluble or partly soluble in the medium, so most oxidations are carried out in aqueous media. The use of water means that several Cr(VI) species are present, however. At high dilution, the excess of water shifts the overall equilibrium towards dichromate.^{23,24} At high concentrations (less water), polymeric chromium trioxide (polychromates) and chromic acid are the predominate species.²⁴ Dichromate is generated by "complex formation between the two acid chromate ions to give a dichromate anion".²⁵ Formation of this complex and its relative concentration are dependent on the pK_a of the acid. In dilute solution the concentration of Cr(VI) is independent of the acid, but only if the acidity is below the apparent pK_a of chromic acid.²⁵ Modification of the acid will increase the pK_a of the complex as the electron-withdrawing power of the acid decreases. The electrons on the oxygen atoms attached to chromium are less available for protonation,²⁵ leading to a larger dissociation constant,²⁶ which suggests that the position of the equilibrium depends on the acid. Indeed, adding a different acid (HA) to the mixture will influence the position of the overall equilibrium according to the reaction:²⁷

$$HCrO_4^- + 2 H^+ + A^- \longrightarrow HCrO_3A + H_2O$$

If the acid is more effective at withdrawing electrons from the complex (HCrO₃A), the pK_a for the reaction increases. There is, therefore, a correlation with the strength of the mineral acid and the HCrO₃A species:^{25,26}

 $H_3PO_4 \ < \ HCl \ < \ H_2SO_4 \ < \ HClO_4$

^{21.} Wiberg, K.B. in chapter 2 of *Oxidation in Organic Chemistry, Part A*, Wiberg, K.B. (Ed.), Academic Press, New York, *1965*, pp 69-70.

 ⁽a) Byström, A.; Wilhelmi, K.A. Acta Chem. Scand. 1950, 4, 1131; (b) Hanic, F.; Stempelóv, D. Chem. Zvestii 1960, 14, 165 [Chem. Abstr. 54: 20402a 1960].

 ⁽a) Reference 21a, pp 71; (b) Neuss, J.D.; Rieman, W. J. Am. Chem. Soc. 1934, 56, 2238; (c) Tong, J.Y.P.; King, E.L. Ibid. 1953, 75, 6180; (d) Davies, W.G.; Prue, J.E. Trans. Faraday Soc. 1955, 51, 1045; (e) Howard, J.R.; Nair, V.S.K.; Nancollas, G.H. Ibid. 1958, 54, 1034; (f) Schwarzenbach, G.; Meier, J. J. Inorg. Nuc. Chem. 1958, 8, 302; (g) Bailey, N.; Carrington, A.; Lott, K.A.K.; Symons, M.C.R. J. Chem. Soc. 1960, 290; (h) Sasaki, Y. Acta Chem. Scand. 1962, 16, 719.

^{24.} Freedman, M.L. J. Am. Chem. Soc. 1958, 80, 2072.

^{25.} Lee, D.G.; Stewart, R J. Am. Chem. Soc. 1964, 86, 3051.

^{26.} Reference 16a, p 72.

^{27. (}a) Boyd, R.H. J. Am. Chem. Soc. 1961, 83, 4288; (b) Boyd, R.H. J. Phys. Chem, 1963, 67, 737.

The nature of the oxidizing species is obviously important for determining the mechanism of oxidation of an alcohol to a carbonyl with chromium (VI). As mentioned above, in aqueous solutions CrO_3 generates $\text{CrO}_4^{2^-}$, HCrO_3^- and $\text{HCr}_2\text{O}_7^{2^-}$ as the primary oxidizing species, along with other chromium species.²⁸ At pH \geq 1, CrO₃ is almost completely ionized.²⁸ Since organic molecules are being oxidized with chromium reagents, the focus tends to be on the organic molecule (the alcohol in this case) and Wiberg presented the following scheme to represent the oxidation of a secondary alcohol to a ketone:²⁹

R ₂ CHOH	+	Cr(VI)		R ₂ C=O	+	Cr(IV)
R ₂ CHOH	+	Cr(IV)		R ₂ COH	+	Cr(III)
R ₂ COH	+	Cr(VI)		R ₂ C=O	+	Cr(V)
R ₂ CHOH	+	Cr(V)		R ₂ C=O	+	Cr(III)
R ₂ CHOH	+	Cr(VI)	3	R ₂ C=O	+ 2	Cr(III)

[Reprinted with permission from Wiberg, K.B.; Mukerjee, S.K. J. Am. Chem. Soc. 1974, 96, 1884. Copyright © 1974 American Chemical Society.]

This mechanism shows that Cr(VI), Cr(IV) and Cr(V) species are involved in the overall oxidation process. Clearly, this is not a balanced equation and the Cr species are undefined. The Cr(VI) species are usually $HCrO_4^-$ and CrO_3 , the Cr(V) is usually $HCrO_4^-$ and the Cr(IV) is usually $HCrO_3^-$.²⁹ The oxidation involves both water (H₂O) and an acid catalyst (H⁺), and a balanced equation for the oxidation of 2-propanol is²⁸

$$3 \underbrace{OH}_{+} + 2 \operatorname{HCrO}_{4^{-}} + 8 \operatorname{H}^{+} \longrightarrow 3 \underbrace{O}_{+} + 2 \operatorname{Cr}^{+3} + 8 \operatorname{H}_{2}O$$

There is strong evidence that the oxidation begins by formation of a chromate ester,³⁰ which collapses to the carbonyl compound and a Cr(IV) species in the rate-determining step.^{28,31,32} The driving force of the reaction is reduction of Cr(VI) to Cr(IV).³³ Westheimer determined that the rate term for the oxidation of 2-propanol was³² $v = k_a [HCrO_4^-] [R_2CHOH] [H^+] + k_b [HCrO_4^-] R_2CHOH] [H^+]^2$. If sulfuric acid is used as the acid in an aqueous medium

^{28. (}a) Westheimer, F.H.; Nicolaides, W. J. Am. Chem. Soc. 1949, 71, 25; (b) Westheimer, F.H. Chem. Rev. 1949, 45, 419 (see p 427).

^{29. (}a) Wiberg, K.B.; Mukerjee, S.K. J. Am. Chem. Soc. 1974, 96, 1884; (b) Rahman, M.; Roĉek, J. Ibid. 1971, 93, 5462, 5455.

^{30. (}a) Reference 21, p 161 and references cited therein; (b) Kläning, U. Acta Chem. Scand. 1957, 11, 1313 and *Ibid.* 1958, 12, 576.

^{31.} Brownell, R.; Leo, A.; Chang, Y.W.; Westheimer, F.H. J. Am. Chem. Soc. 1960, 82, 406.

^{32. (}a) Westheimer, F.H.; Novich, A. J. Chem. Phys. **1943**, 11, 506; (b) Reference 21, see p 159 and reference 102 cited therein.

^{33.} Reference 21, p 167.

containing chromium trioxide and 2-propanol, the initial chromate ester is probably 1, which arises from reaction of $HCrO_4^-$ and H_2SO_4 (HA in the above equation).²⁵ In water containing no external acid, the chromate ester probably takes the form *i*-PrOCrO₃H.³⁴

$$\rightarrow \text{OCrO}_3\text{H} \xleftarrow{\text{HCrO}_4^-} \rightarrow \text{OH} \xrightarrow{\text{HOCrO}_2\text{OSO}_3^-} \xrightarrow{\text{O}} \text{O-}_{\text{Cr}}^{\text{H}} \text{OSO}_3^-$$

Decomposition of chromate ester *i*-PrOCrO₃H involves removal of the proton attached to the oxygen-bearing carbon. Westheimer initially proposed that water behaves as a base to remove this hydrogen,^{31,32,35c} although later work showed that addition of pyridine to the reaction (a stronger base than water) did *not* enhance the rate of oxidation.³⁵ At least two mechanisms have been proposed for this step. Westheimer proposed an intermolecular attack by water as mentioned (see **2**), but later retracted this proposal.^{35c,36} Kwart and Francis³⁴ proposed an intramolecular reaction for removal of the proton (see **3**), by an oxygen on the chromate ester. Roĉek discounted both mechanisms for several reasons, including the important observation that protonation should *not* lead to rate enhancement with a species such as **3**, but in fact it does. Roĉek proposed the mechanism shown for **4**,^{35b} in which oxygen atoms from the chromic acid removed hydrogens both from carbon and from oxygen. Roĉek later proposed³⁷ formation of a coordination complex such as **5** (shown exactly as reported in the paper), presumably formed from Cr(IV) in a similar way to **5**, that decomposed to a radical species (**6**). Further oxidation of **6** generated the products.



There is a steric component to this reaction. As the steric bulk around the carbon bearing the OH group increases, removing that hydrogen becomes increasingly difficult and the overall

37. Rahman, M.; Roĉek, J. J. Am. Chem. Soc. 1971, 93, 5455.

^{34.} Reference 21, p 162.

 ⁽a) Roĉek, J.; Krupicka, J. Chem & Ind. (London) 1957, 1668; (b) Roĉek, J. Collect. Czech. Chem. Commun. 1960, 25, 1052; (c) Westheimer, F.H.; Chang, Y.W. J. Phys. Chem. 1959, 63, 438.

^{36.} Kwart, H.; Francis, P.S. J. Am. Chem. Soc. 1959, 81, 2116.

rate of oxidation will be diminished.³⁸ The relative rate of oxidation of endo-borneol (see 7) compared to exo-borneol (see 8), for example, is $25.0:49.1.^{39a}$ This difference is correlated with the more facile removal of H_a from chromate ester complex 7 (where H_a is on the exo face) than from complex 8 (where is H_a is on the more hindered endo face). Another example of steric hindrance can be seen in cyclohexyl derivatives by comparing *cis-2-tert*-butylcyclohexanol (9, relative rate 50.6) and *trans-2-tert*-butylcyclohexanol (10, relative rate 10.7).^{39a} In both 9 and 10, the bulky *tert*-butyl group will occupy an equatorial position in the lowest energy conformation (sec. 1.5.D). Removal of the equatorial H_a from the chromate ester of 9 is inhibited by a large steric interaction with the adjacent *tert*-butyl group (*G* strain, sec. 1.5.D). This rate difference is also observed with modified chromium reagents such as pyridinium chlorochromate (sec. 3.2.B.ii).^{39b}



From this discussion, it is apparent that oxidation of alcohols with Cr(VI) depends on several factors. The solvent and any acidic additives (or acidic solvents) will influence the rate of the oxidation, as will the structure of the alcohol. It is therefore not surprising that there are many variations in reaction conditions for Cr(VI) oxidations of alcohols. As the substrate and the oxidizing requirements of the chromium are changed, the reaction medium will be changed. Reaction conditions for the oxidation of alcohols are to modify so that the acid is added to the medium. Indeed, chromium trioxide will have different oxidizing abilities in different acids (see above) since different structural entities may be present. Since most organic compounds are insoluble in water, a co-solvent is usually required to dissolve both the chromium reagent and the alcohol substrate. This solvent must be resistant to oxidation so acetic acid or acetone is commonly used. For the alcohol \rightarrow carbonyl conversion several Cr(VI) reagents can be used, including chromium trioxide in water or aqueous acetic acid catalyzed by mineral acid, sodium dichromate in aqueous acetone catalyzed by mineral acid, sodium dichromate in acetic acid, the CrO₃•pyridine complex, and *tert*-butyl chromate.⁴⁰ Primary and secondary alcohols are oxidized to the aldehyde or ketone, respectively. Aldehydes may be oxidized to the carboxylic acid under some conditions.

3.2.A.ii. Chromium Trioxide in Water or Aqueous Acetic Acid. Low molecular weight alcohols are usually sufficiently soluble in water that no co-solvent is required for oxidation

^{38.} Reference 21, p 165.

^{39. (}a) Reference 21, p 166; (b) Suggs, J.W., Ph.D. Thesis Harvard Univ., 1976, Chapter III (see Dissertation Abstracts On-Line).

^{40.} Reference 21, p 142.

with chromium reagents. Oxidation of 2-propanol in water gives excellent yields of acetone, although the miscibility of acetone in water makes its isolation difficult. The presence of other oxidizable groups on the organic substrate such as alkenes, sulfides, phenolic, and amines can lead to side reactions in the oxidation of water soluble alcohols, significantly lowering the yield of carbonyl products. Sulfides are oxidized to sulfoxides, amines to hydroxylamines, and phenols to quinones, for example. Phenylalkyl carbinols are subject to oxidative cleavage with chromium trioxide in aqueous acid, as observed in the oxidation shown.⁴¹ When the R group is isopropyl (*i*-Pr), only 6% cleavage was observed, but changing R to *tert*-butyl led to 60% cleavage, presumably due to greater facility for generating a tertiary cation in the latter case.⁴¹ Cleavage of this type is greatly suppressed by addition of manganous ion. Small amounts of cleavage products can be observed with hindered carbinols, but this is a problem only when a stable carbocation can be produced.⁴²

Oxidation of primary alcohols leads to aldehydes in moderate to good yield. Aldehydes are relatively easy to oxidize to the corresponding carboxylic acid, however. In most cases, the oxidation can be stopped at the aldehyde, but small amounts of the acid are a common byproduct. Heating and long reaction times lead to increased amounts of the acid, and in some cases the aldehyde is the minor product. Where feasible, removal of the aldehyde as it forms will minimize side reactions. When the reaction is pushed to give the carboxylic acid, there are at least two reasonable mechanistic rationales for this conversion.⁴³ Both mechanisms involve formation of a chromate ester. Removal of the α -hydrogen (analogous to the alcohol to aldehyde conversion) either by an external base (as in **11**), or intramolecularly (as in **12**),

generates the carboxylic acid. This oxidation may also occur by initial formation of a hydrate,

^{41. (}a) Reference 21, p 143 and reference 4 therein; (b) Hampton, J.; Leo, A.; Westheimer, F.H. *J. Am. Chem. Soc. 1956*, *78*, 306.

^{42.} Lee, D.G. in Oxidation, Vol 1, Augustine, R.L (Ed.), Marcel Dekker, New York, 1969, p 58.

^{43.} Reference 21, p 174.

followed by removal of the α -hydrogen from 13. This mechanism gives the acid moiety, although a radical process that generates 14 is also possible.⁴³

With some primary alcohols, it is possible to establish an equilibrium between the initially formed aldehyde and the precursor alcohol, in which unreacted alcohol is converted to an hemiacetal (**15**), which can be further oxidized to an ester.⁴⁴ This transformation is often observed in the oxidation of lower molecular weight primary alcohols. Oxidation of 1-butanol to butyl butyrate with Cr(VI), for example, is an *Organic Syntheses* preparation.⁴⁵

$$RCH_{2}OH + Cr^{(VI)} \longrightarrow RCHO$$

$$RCH_{2}OH + RCHO \longrightarrow RHC^{VI}_{15}OCH_{2}R$$

$$OH_{RHC^{VI}_{OCH_{2}R}} + Cr^{(VI)} \longrightarrow RCO_{2}CH_{2}R$$

Some of the problems that accompany oxidation in water can be alleviated or moderated by using an organic co-solvent. Oxidation in aqueous acetic acid will suppress the oxidative cleavage to some extent, as well as greatly improving the solubility of the organic substrate. It is possible to oxidize a wider variety of alcohols in this solvent. Bowman found that CrO_3 in anhydrous acetic acid was superior to CrO_3 in aqueous acetic acid for the oxidation of saturated alcohols. Oxidation of allylic alcohols in anhydrous acetic acid gave yields that were comparable to those obtained in aqueous media.⁴⁶ This improvement may be due to formation of an acetyl chromate ion (AcOCrO₃⁻), analogous to chromate complexes formed with other acids (see HCrO₃A see above). Such a species may increase the electron accepting power of chromium.^{25,47}

$$H_2CrO_4 + AcOH \implies AcOCrO_3^- + H_2O$$

^{44. (}a) Reference 21, p 143; (b) Mosher, W.A.; Preiss, D.M. J. Am. Chem. Soc. 1953, 75, 5605.

^{45.} Robertson, G.R. Org. Synth. Coll. Vol. 1 1941, 138.

^{46. (}a) Reference 21, p 152; (b) Bowman, M.I.; Moore, C.E.; Deutsch, H.R.; Hartman, J.L. *Trans. Kentucky Acad. Sci.* **1953**, *14*, 33 [*Chem. Abstr.* 48:1250b **1954**].

^{47. (}a) Cohen, M.; Westheimer, F.H. J. Am. Chem. Soc. 1952, 74, 4387; (b) Symons, M.C.R. J. Chem. Soc. 1963, 4331.

3.2.A.iii. Chromium Trioxide in Acetone: Jones Oxidation. Organic solvents other than acetic acid can be used with aqueous chromium trioxide. Jones used acetone as a co-solvent in a dilute sulfuric acid solution, and found that oxidation of alkynyl carbinols was improved when compared to other procedures known at that time. Secondary alcohols are oxidized to ketones, and primary alcohols can be oxidized to either an aldehyde or a carboxylic acid. This chromium trioxide/acetone/sulfuric acid reagent is often referred to as the **Jones reagent**, and oxidation of alcohols with this reagent is called **Jones oxidation**.⁴⁸ Jones oxidation is especially useful for molecules that contain alkenyl or alkynyl groups.⁴⁹ Oxidation of alcohols is usually faster in acetone than in acetic acid, and using a large excess of acetone protects the ketone product from further oxidation.⁵⁰ An example is the oxidation of **16** to give ketone **17** in 67% yield, taken from a synthesis of dysidiolide by Forsyth and Demeke.⁵¹ Note that in this oxidation, the secondary alcohol was oxidized to the ketone and the primary alcohol to an acid is also seen in the oxidation of **18** to **19**, in Crimmins and Vanier's



synthesis of the microbial metabolite designated SCH 351448.⁵² Many primary alcohols are oxidized to aldehydes with this procedure,⁵³ but the reaction conditions are strongly acidic and the final product is sometimes a carboxylic acid. However, there are many examples in which Jones oxidation has been used in the presence of reactive functional groups. If the starting material is an aldehyde rather than an alcohol, Jones oxidation gives the carboxylic acid. An example is seen in Hu and Panek's synthesis of (–)-motuporin, in which aldehyde (**20**) was

^{48.} The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-49.

 ⁽a) Heilbron I.; Jones, E.R.H.; Sondheimer, F. J. Chem. Soc. 1949, 604; (b) Haynes, L.J.; Heilbron I.; Jones, E.R.H.; Sondheimer, F. *Ibid.* 1947, 1583; (c) Heilbron I.M.; Jones, E.R.H.; Sondheimer, J. *Ibid.* 1947, 1586.
 Reference 21, p. 145.

^{50.} Reference 21, p 145.

^{51.} Demeke, D.; Forsyth, C.J. Tetrahedron 2002, 58, 6531.

^{52.} Crimmins, M. .; Vanier, G.S. Org. Lett. 2006, 8, 2887.

 ⁽a) Hurd, C.D.; Meinert, R.N. Org. Synth. Coll. Vol. 2, 1943, 541; (b) Fossek, W. Monatsh 1881, 2, 614 and 1883, 4, 660; (c) Bouveault, L.; Rousset, L. Bull. Soc. Chim. Fr. 1894, 11, 300; (d) Jacobson, M. J. Am. Chem. Soc. 1950, 72, 1489; (e) Sauer, J. Org. Synth. Coll. Vol. 4 1963, 813.

oxidized to the acid, **21** in 88% yield.⁵⁴ Jones oxidation is compatible with complex molecules that contain a variety of functional groups such as alkenes, tertiary alcohols, esters, ketones, oxetanes and amides.⁵⁵



3.2.B. Modified Chromium (VI) Oxidants

Apart from changing the solvent, additives can be included in the reaction medium to create a new oxidizing reagent *in situ*. The fundamental Cr(VI) reagent can also be chemically modified prior to being used as an oxidizing agent. This section will examine both of these approaches.^{57a}

3.2.B.i. Chromium Trioxide-Pyridine. In 1948, Sisler and co-workers isolated and characterized a stable complex from the reaction of chromium trioxide and pyridine.^{56b} Sisler did not use this reagent for the oxidation of organic molecules, but Sarett and co-workers recognized its utility in the synthesis of steroids. In this connection, alcohol **22** was oxidized to **24** in 89% yield.⁵⁷ The reagent, which probably has the trigonal bipyramidal structure shown in **23**, proved useful for the general oxidation of primary and secondary alcohols even in the presence of double bonds and thioethers. The oxidation usually requires pyridine as a solvent and was referred to as **Sarett oxidation**⁵⁸ for many years. Care must be exercised in preparing the reagent.



The solution "must always be prepared by cautious addition of chromium trioxide to pyridine which has been carefully purified by distillation from potassium permanganate."⁵⁹ Reversing this order of addition may cause the mixture to ignite spontaneously.⁶⁰

55. Magri, N.F.; Kingston, D.G.I. J. Org. Chem. 1986, 51, 797.

- 57. Poos, G.I.; Arth. G.E.; Beyler, R.E.; Sarett, L.H. J. Am. Chem. Soc. 1953, 75, 422.
- 58. The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-83.

^{54.} Hu, T.; Panek, J.S. J. Am. Chem. Soc. 2002, 124, 11368.

^{56. (}a) For a review of alcohol oxidation using oxochromium(VI)-amine reagents, see Luzzio, F.A. Org. React. **1998**, 53, 1; (b) Sisler, H.H.; Bush, J.D.; Accountius, O.E. J. Am. Chem. Soc. **1948**, 70, 3827.

^{59.} Reference 42, p 60.

^{60.} Holum, J.R. J. Org. Chem. 1961, 26, 4814.

A second problem with Sarett oxidation is difficulty in isolating the products from a pyridine solution. An advantage of the technique, as mentioned above is that alkenes, ketals, sulfides, and tetrahydropyranyl ethers are oxidized much slower than alcohols and rarely give competitive side reactions.⁶¹ Oxidation of secondary alcohols is usually facile, but oxidation of primary aliphatic alcohols often gives low yields of the aldehyde.⁶² Benzylic and allylic alcohols give good yields, however. An example is taken from Kelly and co-worker's synthesis of louisianin C,⁶³ in which benzylic alcohol **25** was treated with chromium trioxide in pyridine at room temperature to give a 75% yield of louisianin C, **26**.



A modification introduced by Collins et al.⁶⁴ was applied to the oxidation of alcohols, and has come to be known as **Collins oxidation**. This modification was developed to deal with the problem of poor yields in the oxidation of primary alcohols to aldehydes, and to improve the isolation of the carbonyl products. The Sisler-Sarett reagent formed by reaction of chromium trioxide and pyridine was first removed from the pyridine solvent and added to dichloromethane, and this mixture was then treated with the alcohol. The oxidation typically required a 5:1 or 6:1 ratio of complex/alcohol, and reaction occurred at ambient temperatures.⁶⁴ Cyclohexanol was oxidized to cyclohexanone in 98% yield by this method, and 1-heptanol was oxidized to heptanal in 93% yield. The yield of aldehyde products from primary alcohols was significantly better, but a large excess of the reagent was required and the isolation problems persisted. Nonetheless, Collins oxidation became a mainstay of organic synthesis. An example is taken from the synthesis of hybocarpone, by Nicolaou and Gray,⁶⁵ in which oxidation of **27** gave ketone 28 in 86% yield. Allylic alcohols are easily oxidized to the corresponding conjugated ketone or aldehyde with this reagent, and Urones and co-workers used this type of oxidation in a synthesis of (-)-hyrtiosal.⁶⁶ This reagent can be used with groups that are more sensitive to hydrolysis or to over-oxidation. These include lactols, as illustrated by Ando and co-worker's conversion of lactol 29 to lactone 30.67 Ratcliffe and co-workers further improved this procedure by preparing dichloromethane solutions of the chromium trioxide-pyridine complex directly.⁶⁸

^{61.} Reference 21, pp 154-158.

^{62.} Korytnyk, W.; Kris, E.J.; Singh, R.P. J. Org. Chem. 1964, 29, 574.

^{63.} Beierle, J.M.; Osimboni, E.B.; Metallinos, C.; Zhao, Y.; Kelly, T.R. J. Org. Chem. 2003, 68, 4970.

^{64.} Collins, J.C.; Hess, W.W.; Frank, F.J. Tetrahedron Lett. 1968, 3363.

^{65.} Nicolaou, K.C.; Gray, D.L.F. J. Am. Chem. Soc. 2004, 126, 607.

^{66.} Basabe, P.; Diego, A.; Díez, D.; Marcos, I.S.; Urones, J.G. Synlett 2000, 1807.

 ⁽a) Ando, M.; Akahane, A.; Takase, K. Bull. Chem. Soc. Jpn. 1978, 51, 283; (b) Ando, M.; Tajima, K.; Takase, K. Chem. Lett. 1978, 617.

^{68.} Ratcliffe, R.; Rodehorst, R. J. Org. Chem. 1970, 35, 4000.

The procedure typically used today is addition of chromium trioxide to dichloromethane and pyridine, followed by addition of the alcohol, but it is still referred to as Collins oxidation.



3.2.B.ii. Pyridinium Chlorochromate. The need for improved selectivity in the oxidation of primary alcohols, and greater ease for isolation of products prompted further research into the nature of Cr(VI) reagents. Corey and Suggs found that addition of pyridine to a solution of chromium trioxide in aqueous HCl led to crystallization of a solid reagent (**31**, pyridinium chlorochromate or **PCC**).⁶⁹ In dichloromethane, this reagent was superior for the conversion of primary alcohols to aldehydes, but less efficient than the Collins oxidation when applied to allylic alcohols.⁷⁰ Oxidation of 1-heptanol with PCC in dichloromethane gave 78% of heptanal. A synthetic example is taken from Corey and Hong's synthesis of arborone, in which **32** was oxidized by PCC to the ketone (**33**) in 82% yield.⁷¹ As stated by Corey, PCC is an effective oxidant in dichloromethane although aqueous chlorochromate species are not very effective oxidants.⁷⁰ Oxidation of secondary alcohols to ketones is straightforward.



A drawback to the use of pyridinium chlorochromate is its mild acidity (note the use of sodium acetate to buffer the oxidation of **32** to **33**). It is inferior to Collins oxidation when the oxidation products or the starting alcohol is acid sensitive. This acidity can be used to synthetic advantage, however, and Corey described its use to promote oxidative cationic cyclizations.⁷² Reaction of citronellol with PCC in dichloromethane was accompanied by cationic cyclization reaction

^{69.} Corey, E.J.; Suggs, J.W. Tetrahedron Lett. 1975, 2647.

^{70. (}a) Banerji, K.K. Bull Chem. Soc. Jpn. 1978, 51, 2732; (b) Banerji, K.K. J. Chem. Soc. Perkin Trans. 21978, 639.

^{71.} Hong, S.; Corey, E.J. J. Am. Chem. Soc. 2006, 128, 1346.

^{72.} Corey, E.J.; Boger, D.L. Tetrahedron Lett. 1978, 2461.

to give (–)-pulegone.^{73a,69} Oxidative transpositions can also occur.73b In studies toward a synthesis of guanacastepene A,⁷⁴ Mehta and Umarye oxidized of a mixture of **34** and **35** with PCC to give a 90% yield of the rearranged ketone **36**. Oxidations using PCC on alumina⁷⁵ have also been reported, presumably to minimize acid-catalyzed rearrangement. The PCC reagent has been used for the conversion of oximes to ketones,⁷⁶ and for the direct oxidation of tetrahydropyranyl protected alcohols to aldehydes.⁷⁷



3.2.B.iii. Pyridinium Dichromate. Problems caused by the acidity of PCC can be largely eliminated, by using the more neutral reagent pyridinium dichromate (PDC) 37. Although first used by Coates and Corrigan⁷⁸ it was not exploited synthetically until Corey prepared the reagent by addition of pyridine to neutral chromium trioxide solutions and used it for the oxidation of alcohols to aldehydes, ketones, and acids.⁷⁹ The reagent is not acidic and the neutral conditions required for the oxidation are superior for the oxidation of allylic alcohols. In dichloromethane (non-aqueous workup) the oxidation is similar to that of PCC. Addition of catalytic amounts of pyridinium trifluoroacetate in dichloromethane significantly increases the rate of oxidation. Allylic alcohols are oxidized faster than aliphatic alcohols, making PDC the reagent of choice for this transformation. Cyclohexenol, for example, is oxidized 10 times faster than cyclohexanol with PDC in dichloromethane at 25°C.79 Primary aliphatic alcohols are also oxidized under very mild conditions.⁸⁰ This oxidation occurs under essentially neutral conditions, as shown by the reaction of **38** with PDC to give aldehyde **39** in 92% yield, despite the presence of the acid sensitive enol ether.⁷⁹ A synthetic example is taken from Nemoto and co-worker's synthesis of macrosphelide B,⁸¹ in which the allylic secondary alcohol unit in 40 was oxidized to conjugated ketone 41, in 82% yield using PDC in dichloromethane.

- 76. Maloney, J.R.; Lyle, R.E.; Saavedra, J.E.; Lyle, G.G Synthesis 1978, 212.
- 77. Sonnet, P.E. Org. Prep. Proceed. Int. 1978, 10, 91.
- 78. Coates, W.M.; Corrigan, J.R. Chem. Ind. 1969, 1594.
- 79. Corey, E.J.; Schmidt, G. Tetrahedron Lett. 1979, 399.
- 80. Boeckman, Jr., R.K.; Perni, R.B. J. Org. Chem. 1986, 51, 5486.
- 81. Kawaguchi, T.; Funamori, N.; Matsuya, Y.; Nemoto, H. J. Org. Chem. 2004, 69, 505.

 ⁽a) Corey, E.J.; Ensley, H.E.; Suggs, J.W. J. Org. Chem. 1976, 41, 380; (b) Dauben, W.G.; Michno, D.M. J. Org. Chem. 1977, 42, 682. Also see, (c) Corey, E.J.; Ha, D.C. Tetrahedron Lett. 1988, 29, 3171; (d) Waddell, T.G.; Carter, A.D.; Miller, T.J.; Pagni, R.M. J. Org. Chem. 1992, 57, 381; (e) Luzzio, F.A.; Guziec, Jr., F.S. Org. Prep. Proceed. Int. 1988, 20, 533; (f) Schlecht, M.F.; Kim, H.-J. J. Org. Chem. 1989, 54, 583.

^{74.} Mehta, G.; Jayant D. Umarye, J.B. Org. Lett. 2002, 4, 1063.

^{75.} For an example taken from a synthesis see Moreno-Dorado, F.J.; Guerra, F.M.; Aladro, F.J.; Bustamante, J.M.; Jorge, Z.D.; Massanet, G.M. J. Nat. Prod. 2000, 63, 934.



There can be a significant difference in product formation in the oxidation of aliphatic primary alcohols versus that of allylic primary alcohols, when the solvent is DMF. Cyclohexenol is oxidized to cyclohexenone in 86% yield with PDC in DMF at 0°C.⁷⁹ Similarly, geraniol was oxidized to geranial in 92% yield. However, treatment of non-conjugated primary alcohols with PDC in DMF (ambient temperature) often gave carboxylic acids rather than an aldehyde. For example, in Cossy and co-worker's synthesis of zoapatanol,⁸² oxidation of **42** with PDC in DMF at 25°C gave hydroxy-acid **43**, which cyclized to lactone **44** in greater than 85% yield. Aldehydes can also be oxidized to the carboxylic acid, as in Williams and Jain's synthesis of (+)-negamycin,⁸³ where the aldehyde unit in **45** was converted to carboxylic acid **46** in 97% yield.



3.2.B.iv. Structurally Modified Chromium Reagents. The literature is full of chromium trioxide complexes developed by adding amine or phosphine bases, usually with the goal of varying the specificity of the oxidation.

Alternatively, stabilized chromate esters have been prepared and found to be effective oxidizing agents. If the oxidizing power of these modified reagents can be generalized at all, it may be said

^{82.} Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. J. Org. Chem. 2005, 70, 2097.

^{83.} Jain, R.P.; Williams, R.M. J. Org. Chem. 2002, 67, 6361.

they behave similarly to PCC or PDC. Some examples are **47**,⁸⁴ **48**,⁸⁵ **49**,⁸⁶ and **50**,⁸⁷ and **51**.⁸⁸ The reasons for developing modified reagents can vary with the application. In many instances, they were developed to alleviate problems associated with isolation of products, or the use of large excess of the oxidizing reagent (as with Sarett and Collins oxidations). In other cases, the need for decreased acidity, for improved solubility in low-boiling aprotic organic solvents, or for increasing (or decreasing) the relative oxidizing power of the chromium reagent provided the driving force for developing the new reagent. For **47** and **49**, chromyl chloride (CrO₂Cl₂) was the chromium precursor rather than chromium trioxide. Another modification used amine bases other than pyridine, giving the PDC analog **48** and the PCC analog, **50**. Using a phosphine as the base, the bis(phosphine) 1,1-bis(triphenyl)phosphinomethane generated PDC analog **51**. Oxidation with modified chromium reagents is similar to PCC and PDC oxidations. Reagent **49** was developed by Corey and co-workers, and is of particular interest in that it can be used as a *catalytic* oxidizing agent (only 2% of **49** was required for the oxidation of cyclooctanone from cyclooctanol) in the presence of peroxyacetic acid (in dichloromethane).⁸⁶



The functional group transforms for the oxidations in this section are

3.2.C. Dimethyl Sulfoxide and Related Oxidations⁸⁹

Section 3.2.B.iv discussed the oxidation of alcohols using derivatives of the transition metal Cr(VI), which often required acidic conditions. Many alcohols, especially those bearing sensitive functional groups, require neutral oxidizing conditions. The development of PDC and related reagents helped to alleviate this problem, but PCC is an acidic reagent. There are cases where PDC or PCC give poor yields, especially with hindered alcohols. The key to Cr(VI) oxidations was formation of a chromate ester and removal of the acidic α -hydrogen (as

88. Cristau, H.-J.; Torreilles, E.; Morand, P.; Christol, H. Tetrahedron Lett. 1986, 27, 1775.

^{84.} Sharpless, K.B.; Akashi, K. J. Am. Chem. Soc. 1975, 97, 5927.

^{85.} López, C.; González, A.; Cossío, F.P.; Palomo, C. Synth. Commun. 1985, 15, 1197.

^{86.} Corey, E.J.; Barrette, E.P.; Magriotis, P.A. Tetrahedron Lett. 1985, 26, 5855.

^{87. (}a) Davis, H.B.; Sheets, R.M.; Brannfors, J.M.; Paudler, W.W.; Gard, G.L. *Heterocycles* 1983, 20, 2029; (b) Firouzabadi, H.; Iranpoor, N.; Kiaeezadeh, F.; Toofan, J. *Tetrahedron* 1986, 42, 719.

Moffatt, J.G. in *Oxidation*, Vol 2, Augustine, R.L.; Trecker, D.J. (Eds.), Marcel Dekker Inc., New York, 1971, pp. 1-64.



in **52**). In one sense, the chromate ester behaved as a leaving group and removal of the hydrogen that is β to the chromium makes the reaction *conceptually* analogous to an E2 reaction (sec. 2.9.A). The problem with this analogy is, of course, that there

is no direct evidence for removal of the hydrogen in **52** by an external base.^{34,35} Removal of the hydrogen via an intramolecular process is also viable, as in **53**, and this has a close analogy to the syn-elimination discussed in section 2.9.C. Reagents other than Cr(VI) can be used to oxidize alcohols. It has been shown by a number of workers that DMSO-based reagents form a sulfoxonium intermediate, where the β -hydrogen can be removed, and dimethyl sulfide (Me₂S, abbreviated DMS) functions as the leaving group. This overall process leads to oxidation of alcohols and there are many variations of this reaction.

Dimethyl sulfoxide functions as both a solvent and a reactant for a variety of alcohol substrates. The nucleophilic oxygen can react with electrophilic centers to form a sulfoxonium salt, which gives ketones or aldehydes under neutral conditions. Kornblum et al. first observed this process, but with halides rather than with alcohols. He reported that reaction of α -halo ketones with DMSO at elevated temperatures gave good yields of the corresponding glyoxal

Ph Br $DMSO > 100^{\circ}C$ Ph 54 54 55	о Ц сно 55
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(an α -keto-aldehyde).⁹⁰ By this procedure, phenylacetyl bromide (**54**) was oxidized to **55** in 71% yield⁹⁰ in what has been called the **Kornblum aldehyde synthesis**.⁹¹ The contact times were usually very short, and if the glyoxal could be removed from the reaction medium by

distillation as it was formed the reaction was very efficient. It was often difficult to isolate high boiling glyoxals from DMSO, however. This transformation is not limited to α -halo ketones. Primary⁹² and secondary⁹³ alkyl iodides or tosylates can be converted to aldehydes or ketones, although they are much less reactive than α -halo ketones. Reaction of 1-bromooctane with DMSO and NaHCO₃ at 100°C, for example, gave octanal in 74% yield after 5 minutes.⁹² This outcome can be compared with the conversion of an alkyl tosylate to a ketone, which required temperatures of 150-170°C and the presence of an acid receptor such as sodium bicarbonate. Elimination is a serious side reaction, and attempts to oxidize secondary α -halo ketones often give poor yields.⁹⁴ The mechanism probably involves nucleophilic displacement of halides by

^{90.} Kornblum, N.; Powers, J.W.; Anderson, G.J.; Jones, W.J.; Larson, H.O.; Levand, O.; Weaver, W.M. J. Am. Chem. Soc. 1957, 79, 6562.

^{91.} Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 376-377.

^{92. (}a) Kornblum, N.; Jones, W.J.; Anderson, G.J. J. Am. Chem. Soc. 1959, 81, 4113; (b) Nace, H.R.; Monagle, J.J. J. Org. Chem. 1959, 24, 1792.

^{93.} Baizer, M.M. J. Org. Chem. 1960, 25, 670.

^{94. (}a) Jones, D.N.; Saeed, M.A. J. Chem. Soc. 1963, 4657; (b) Iacona, R.N.; Rowland, A.T.; Nace, H.R. J. Org. Chem. 1964, 29, 3495.

DMSO to form an alkoxysulfoxonium salt, **56**. Removal of the α -proton, probably by DMSO, leads to the carbonyl product and DMS (which functions as the leaving group).⁹⁵



A similar type of oxidation was observed when alcohols reacted with DMSO. Traynelis and Hergenrother showed that benzylic and allylic alcohols were converted to the corresponding aldehyde in high yield by refluxing in DMSO, with air bubbling through the medium.⁹⁶ Air was the oxidant, DMSO the solvent and cinnamyl alcohol was oxidized in this manner to cinnamaldehyde in 90% yield.⁹⁶ Despite this example, air or oxygen is not required. A mixture of DMSO and several co-reagents react with alcohols to form a complex that leads to formation of aldehydes and ketones. There are several variations of this fundamental reaction involving DMSO. In each case, a key reagent is added to activate the DMSO-alcohol oxidation reaction. Several variations will be presented.

3.2.C.i. Swern Oxidation. This variation is quite common in synthesis and was discovered by Swern, who found that DMSO can be activated for the oxidation of alcohols by addition of trifluoroacetic anhydride.⁹⁷ The reaction is usually done in dichloromethane at temperatures below -30° C.

In the absence of a moderating solvent, admixture of DMSO and (CF₃CO)₂O proceeds explosively.

The initially formed trifluoroacetyl derivative (**57**) is stable below –°C but at higher temperatures undergoes a **Pummerer rearrangement** to give **58**.⁹⁸ At lower temperatures, the initially formed sulfoxonium intermediate **57** reacts with an alcohol to form **58**, and then loses DMS to form the ketone or aldehyde. This mechanism is common for virtually all of the oxidations presented in this section, but the reagent used to generate **56** varies. An important and interesting feature of Swern oxidation is the low sensitivity to steric encumbrance. Oxidation of the moderately hindered alcohol 2,4-dimethyl-3-pentanol gave 2,4-dimethyl-3-pentanone in 86% yield.⁹⁷ Oxidation of a primary alcohol to the corresponding aldehyde is facile. Amines are commonly added to facilitate decomposition of the initially formed complex. Oxidation of 1-decanol gave a

^{95.} Hunsberger, I.M.; Tien, J.M. Chem. & Ind. 1959, 88.

^{96.} Traynelis, V.J.; Hergenrother, W.L. J. Am. Chem. Soc. 1964, 86, 298.

^{97.} Mancuso, A.J.; Swern, D. Synthesis 1981, 165.

 ^{98. (}a) Sharma, A.K.; Swern, D. *Tetrahedron Lett.* 1974, 1503; (b) Sharma, A.K.; Ku, T.; Dawson, A.D.; Swern, D. J. Org. Chem. 1975, 40, 2758; (c) Pummerer, R. *Berichte* 1910, 43, 1401.

56% yield of decanal when triethylamine was added. Addition of diisopropylamine rather than triethylamine increased the yield to 81%.⁹⁹ Swern oxidation can be used in highly functionalized molecules, and as mentioned it tolerates alcohols that are somewhat sterically hindered.

$$Me^{-\overset{O}{S}}Me \xrightarrow{(CF_{3}CO)_{2}O}_{CH_{2}Cl_{2}} \begin{bmatrix} \overset{O}{O}_{2}CCF_{3} & O \\ Me & & \\ + & S-O & CF_{3} \\ Me' & 57 \end{bmatrix} \xrightarrow{>-30^{\circ}C} Me^{-\overset{O}{S}}Me^{-\overset{O}{S}}S \xrightarrow{O}CF_{3} \\ \xrightarrow{OH} & \overset{R}{H}R & \overset{R}{R} \\ \xrightarrow{H}R & \overset{R}{H}R & \overset{R}{H}R & \overset{R}{H}R \\ \xrightarrow{Me} & \overset{O}{S} \xrightarrow{H}H \xrightarrow{O} & \overset{R}{H}R \\ \xrightarrow{Me} & \overset{S}{S} \xrightarrow{O} & \overset{C}{H}H \xrightarrow{O} & \overset{R}{H}R \\ \xrightarrow{Me} & \overset{S}{S} \xrightarrow{O} & \overset{C}{H}H \xrightarrow{O} & \overset{R}{H}R \\ \xrightarrow{Me} & \overset{S}{S} \xrightarrow{O} & \overset{C}{H}H \xrightarrow{H}H^{-}B^{+} \\ \xrightarrow{Me} & \overset{S}{S} \xrightarrow{O} & \overset{C}{H}H \xrightarrow{O} & \overset{S}{H}H \xrightarrow{O} & \overset{S}{H}H \xrightarrow{H}H^{-}B^{+} \\ \xrightarrow{Me} & \overset{S}{S} \xrightarrow{O} & \overset{S}{H}H \xrightarrow{O} & \overset{S}{H}H \xrightarrow{O} & \overset{S}{H}H \xrightarrow{H}H^{-}B^{+} \\ \xrightarrow{Me} & \overset{S}{S} \xrightarrow{O} & \overset{S}{H}H \xrightarrow{O} & \overset{S}{H$$

Swern also found that oxalyl chloride activates DMSO for the oxidation of alcohols.

Oxalyl chloride and DMSO react violently and exothermically at ambient temperatures.

The resulting reagent is superior to the DMSO-trifluoroacetic anhydride reagent.¹⁰⁰ The reaction probably proceeds via intermediate complex **59**, which is unstable above the preferred reaction temperature of -60° C.

$$Me^{-\overset{O}{\overset{H}{S}}}_{Me} \xrightarrow{Cl}{\overset{O}{\overset{Cl}{\overset{H}{G}}}_{Cl}} \left[\overset{Me}{\overset{H}{\overset{H}{S}}_{-Cl}} \xrightarrow{Cl}{\overset{H}{\overset{H}{G}}_{Cl}} \left[\overset{Me}{\overset{H}{\overset{H}{S}}_{-Cl}} \xrightarrow{Cl}{\overset{H}{\overset{H}{G}}_{Cl}} \right] \xrightarrow{-CO_{2}} \xrightarrow{Me}_{Me^{-}} \xrightarrow{H^{+}{S}}_{S-Cl} \xrightarrow{Cl}{\overset{H}{\overset{H}{G}}_{Me^{-}}} \xrightarrow{Cl}{\overset{H}{\overset{H}{G}}} \xrightarrow{Cl}{\overset{H}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{\overset{H}{G}} \xrightarrow{Cl}} \xrightarrow{Cl}{\overset{H}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G} \overset{H}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G} \overset{H}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G}} \xrightarrow{Cl}{\overset{H}{G} \overset{H}{{G}} \overset{H}{\overset{H}{G}} \overset{Cl}{\overset{H}{G}} \overset{H}{\overset{H}{G} \overset{H}{\overset{H}{G}} \overset{H}{\overset{H}{G} \overset{H}{\overset{H}{G}}$$

The reaction proceeds with loss of both carbon dioxide and carbon monoxide to give chlorosulfonium salt **60**.⁹⁷ When **60** is generated in the presence of an alcohol, **56** is formed and deprotonation gives the carbonyl and dimethyl sulfide. Cyclododecanol was oxidized to cyclododecanone in 97% yield with this reagent, and hex-2-en-1-ol was oxidized to the conjugated aldehyde 2-hexenal in good yield.⁹⁷ Oxidation with DMSO and oxalyl chloride is often called **Swern oxidation**,¹⁰¹ although this term can also be used with the DMSO-trifluoroacetic anhydride oxidation. Note that an odorless Swern oxidation protocol has been developed using dodecyl methyl sulfide.¹⁰²

A typical synthetic use involving oxalyl chloride and DMSO is the conversion of the diol unit in **61** to keto-aldehyde **62** in 74% yield, taken from Ito, Iguchi, and co-worker's synthesis

^{99.} Huang, S.L.; Omura, K.; Swern, D. Synthesis 1978, 297.

 ^{100. (}a) Omura, K.; Swern, D. *Tetrahedron* 1978, 34, 1651; (b) Mancuso, A.J.; Huang, S.-L.; Swern, D. J. Org. Chem. 1978, 43, 2480.

^{101.} The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-92.

^{102.} Ohsugi, S-i.; Nishide, K.; Oono, K.; Okuyama, K.; Fudesaka, M.; Kodama, S.; Node, M. *Tetrahedron* 2003, 59, 8393.

of (+)-tricycloclavulone.¹⁰³ In a synthesis of phorboxazole A by Williams and co-workers,¹⁰⁴ trifluoroacetic anhydride and DMSO was used to oxidize the primary alcohol unit in **63** to aldehyde **64**, in >90% yield. In many synthetic sequences, one will find the term Swern oxidation or simply Swern over a reaction arrow rather than giving the reagents. This is quite common, forcing the reader to recognize certain named reactions.



The functional group transform for DMSO-type oxidations is



3.2.C.ii. Moffatt Oxidation. Another useful DMSO based oxidation predates the Swern oxidation, and uses a mixture of DMSO and dicyclohexylcarbodiimide (DCC, **66**) in the presence of an acid catalyst to generate an intermediate such as **56**.¹⁰⁵ This reaction is known as **Moffatt oxidation**,¹⁰⁵ and an example is the conversion of **65** to **67** (71% yield), used in Smith and co-worker's synthesis of (–)-penitrem D.¹⁰⁶



^{103.} Ito, H.; Hasegawa, M.; Takenaka, Y.; Kobayashi, T.; Iguchi, K. J. Am. Chem. Soc. 2004, 126, 4520.

- 105. Pfitzner, K.E.; Moffatt, J.G. J. Am. Chem. Soc. 1965, 87, 5661.
- 106. Smith III, A.B.; Kanoh, N.; Ishiyama, H.; Minakawa, N.; Rainier, J.D.; Hartz, R.A.; Cho,Y.S.; Cui, H.; Moser, W.H. J. Am. Chem. Soc. 2003, 125, 8228.

^{104.} Williams, D.R.; Kiryanov, A.A.; Emde, U.; Clark, M.P.; Berliner, M.A.; Reeves, J.T. *Angew. Chem. Int. Ed. 2003*, *42*, 1258.

Moffatt provided a mechanistic rationale for this oxidation,^{107,105} where the driving force of the reaction is formation and separation of the highly insoluble dicyclohexylurea (**70**). The initial reaction of DMSO and DCC (**66**) forms sulfoxonium intermediate **68**, which now contains a urea leaving group (see **69**). Alkoxysulfonium intermediate **69** is clearly related to Swern intermediate **57**. When the alcohol attacks the electrophilic sulfur atom, dicyclohexylurea (**70**) is displaced to generate the requisite sulfoxonium salt **56**. Deprotonation of the sulfoxonium salt is probably an intermolecular process, and it generates a sulfur ylid (**71**; sec. 8.8.B) that is stabilized by the *d*-orbitals of sulfur.¹⁰⁸ The carbanion center in **71** probably removes the α -hydrogen intramolecularly (as shown). The intermolecular reaction alternative is also possible (analogous to **56**). By either mechanism, dimethyl sulfide is lost and the aldehyde or ketone is formed. Removal of the hydrogen as suggested by **71** is formally analogous to the synelimination mechanism discussed in section 2.9.C. An alternative mechanism involving complex formation of the alcohol and DCC prior to its reaction with DMSO has not been observed.¹⁰⁹



The initial reaction with DMSO is usually fast, but overall oxidation is quite slow unless mineral acids or strong organic acids are added to the reaction.¹¹⁰ The pyridinium salts of strong acids are also good catalysts, particularly the pyridinium salts of orthophosphoric acid and trifluoroacetic acid. Reagents formed in the presence of these acids gave clean and rapid oxidation of primary and secondary alcohols in the Moffatt oxidation. *o*-Phosphoric acid,¹¹¹ dichloroacetic acid, and pyridinium trifluoroacetate are the most common additives used in this oxidation.¹¹² Moffatt oxidation has several problems associated with it. One is formation of the

111. Pfitzner, K.E.; Moffatt, J.G. J. Am. Chem. Soc. 1963, 85, 3027.

^{107.} Reference 89, p 12.

^{108. (}a) Cilento, G. Chem. Rev. 1960, 60, 147; (b) Johnson, C.R.; Phillips, W.G. J. Am. Chem. Soc. 1969, 91, 682.

^{109.} Reference 89, pp 13-15.

^{110.} Reference 89, p 6.

^{112.} Reference 89, p 7.

urea product **70**, which can be very difficult to separate from the other products. Treatment with oxalic acid is the most common method employed for the removal of the last vestiges of the dicyclohexylurea by-product.¹¹³ Oxidation of homoallylic alcohols is sometimes accompanied by isomerization of the double bond into conjugation with the carbonyl group. This can be minimized or prevented by addition of pyridinium trifluoroacetate. A threefold excess of DCC and an excess of DMSO are usually required for Moffatt oxidation, and these must be removed from the product. The DMSO need not be the solvent, however, and addition of a co-solvent such as ethyl acetate often leads to better results. Despite the drawbacks, Moffatt oxidation is useful in many synthetic applications. Tertiary alcohols are, of course, resistant to Moffatt oxidation but dehydration has been observed in such systems,¹¹⁴ to give the alkene and regenerate DMSO.¹¹⁴ Some steroidal allylic alcohols dehydrate to a heteroannular diene under these conditions.¹¹⁵

3.2.C.iii. Other DMSO Oxidations. Albright and Goldman developed a reagent using DMSO and acetic anhydride that formed an active sulfoxonium complex.¹¹⁶ In the initial work, yohimbine was oxidized to the ketone (yohimbinone) in 85% yield, at ambient temperatures in 24 h.¹¹⁶ As with DCC, DMSO initially reacts with acetic anhydride to form sulfoxonium salt **72**, which then reacts with the alcohol. Acetate is the leaving group attached to sulfur, and reaction with an alcohol generates **56**. The acetate anion serves as the base in this case to

$$Me^{-\overset{O}{S}}Me \xrightarrow{Me} O^{\overset{O}{T}} Me \xrightarrow{Me} Me^{\overset{O}{T}} He^{\overset{O}{T}} He^{\overset{O}{T}}$$

remove the α -proton and generate the ketone or aldehyde. A major advantage of this method is the production of water soluble by-products, and it is especially effective with hindered alcohols. An example, taken from Jeon, Kim and co-worker's synthesis of valienamine,¹¹⁷ is the oxidation of the secondary alcohol **73** to give a 94% yield of **74** in the presence of the dithioacetal unit. With unhindered alcohols the products are often acetate esters and thiomethoxymethyl esters.



^{113.} Reference 89, p 44.

^{114.} Reference 89, p 38.

^{115.} Reference 89, p 39.

^{116.} Albright, J.D.; Goldman, L. J. Am. Chem. Soc. 1967, 89, 2416.

^{117.} Chang, Y-K.; Lee, B.-Y.; Kim, D.J.; Lee, G.S.; Jeon, H.B.; Kim, K.S. J. Org. Chem. 2005, 70, 3299.

Onodera et al. developed a reagent for the oxidation of alcohols using DMSO and phosphorus pentoxide. This method is very efficient for the oxidation the secondary alcohols units found in carbohydrates.¹¹⁸ The alcohol moiety in **75**, for example, was converted to ketone **76** in 65% yield.¹¹⁸ The initial intermediate was probably the sulfoxonium derivative (**77**), which was attacked by the alcohol. Deprotonation of the alkoxy-sulfoxonium ion in the usual manner gave the ketone. Virtually all examples of oxidation with this reagent involved carbohydrates.



The complex formed by pyridine-sulfur trioxide was shown to activate DMSO for oxidation, in the presence of a base such as triethylamine.¹¹⁹ The presumed intermediate is **78**, which reacts with the alcohol to give the usual complex **56**, and deprotonation by triethylamine gives the ketone or aldehyde. Alcohols with different stereochemical and conformational properties can exhibit great differences in their rate of oxidation, which leads to differences in the selectivity for the oxidation of related alcohols. This modification is found in several syntheses of natural products. In Wipf and Spencer's synthesis of tuberostemonine,¹²⁰ oxidation of the allylic alcohol unit in **79** to conjugated ketone **80** was found to be superior (>88% yield) to oxidation with tetrapropylammonium perruthenate (see 3.2.F.i), when done on large scale.



3.2.D. Dess-Martin Periodinane Oxidation



^{118.} Onodera, K.; Hirano, S.; Kashimura, N. J. Am. Chem. Soc. 1965, 87, 4651.

^{119.} Parikh, J.R.; von E. Doering, W. J. Am. Chem. Soc. 1967, 89, 5505.

^{120.} Wipf, P.; Spencer, S.R. J. Am. Chem. Soc. 2005, 127, 225

A mild oxidizing reagents has been developed that contains a hypervalent iodine.¹²¹ Dess and Martin showed that 2-iodobenzoic acid (**81**) reacted with KBrO₃ in sulfuric acid to give a 93% yield of **82**. Subsequent heating to 100°C with acetic anhydride and acetic acid gave **83** in 93% yield, the so-called **Dess-Martin periodinane** [1,1,1-tris(acetyloxy)-1,1-dihydro-1,2-beniodoxo-3-9(1*H*)-one].¹²²

The Dess-Martin reagent can be shock sensitive under some conditions, and it explodes above 200°C.¹²³ An improved procedure for its preparation is available.¹²⁴

Alcohols are readily oxidized to ketones or aldehydes, as in the oxidation of cyclohexanol to cyclohexanone in 90% yield, in dichloromethane at 25°C.¹²² In this particular reaction, an intermediate was trapped and its structure shown to be **84**.¹²² The reagent appears to have an indefinite shelf-life in a sealed container, but hydrolysis occurs upon long-term exposure to atmospheric moisture. Hypervalent iodine reagents are well-known oxidizing agents,¹²⁵ and oxidation of the α -position of methyl ketones to give the corresponding α -hydroxyketone is an important application.¹²⁶ An inert atmosphere is not required, but addition of catalytic amount of trifluoroacetic acid accelerates the oxidation. The catalyst is not required, however. It has also been shown that a Dess-Martin intermediate can be generated in aqueous media and used for oxidation.¹²⁷ Dess and Martin prepared several other periodinane reagents that also oxidizes alcohols,¹²⁸ as well as a chiral hypervalent organoiodinane derived from a chiral binaphthyl.¹²⁹



123. Plumb, J.B.; Harper, D.J. Chem. Eng. News 1990, 68 (No. 29, July 16), p 3.

- 125. Moriarty, R.M.; Prakash, O. Acc. Chem. Res. 1986, 19, 244.
- 126. (a) Moriarty, R.M.; John, L.S.; Du, P.C. J. Chem. Soc. Chem. Commun. 1981, 641; (b) Moriarty, R.M.; Gupta, S.; Hu, H.; Berenschot, D.R.; White, K.B. J. Am. Chem. Soc. 1981, 103, 686; (c) Moriarty, R.M.; Hu, H.; Gupta, S.C. Tetrahedron Lett. 1981, 22, 1283.
- 127. Meyer, S.D.; Schreiber, S.L. J. Org. Chem. 1994, 59, 7549.
- 128. Dess, D.B.; Martin, J.C. J. Am. Chem. Soc. 1991, 113, 7277.
- 129. Ochiai, M.; Takaoka, Y.; Masaki, Y.; Nagao, Y.; Shiro, M. J. Am. Chem. Soc. 1990, 112, 5677.

^{121.} For reactions of hypervalent iodine reagents in the synthesis of heterocyclic compounds, see Prakash, O.; Singh, S.P. *Aldrichimica Acta* **1994**, *27*, 15.

^{122. (}a) Dess, D.B.; Martin, J.C. J. Org. Chem. 1983, 48, 4155. (b) See The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-23.

^{124. (}a) Ireland, R.E.; Liu, L.J. J. Org. Chem. 1993, 58, 2899. Also see, (b) Frigerio, M.; Santagostino, M.; Sputore, S. J. Org. Chem. 1999, 64, 4537.

There are many synthetic applications in the recent literature. The oxidation of a primary alcohol unit in a substrate that can tolerate only a narrow range of reaction conditions, or is part of a highly functionalized molecule is common.¹³⁰ In Paquette and Chang's synthesis of the polyol domain of amphidinol 3,¹³¹ the primary alcohol unit in **85** was oxidized to an aldehyde in **86**, in quantitative yield (BOM = benzyloxymethyl ether). Secondary alcohols are also oxidized under mild conditions.



3.2.E. Oxidation with TEMPO and Oxammonium Salts

Oxammonium salts, such as **87** (**Bobbitt's reagent**),¹³² are useful oxidizing agents for the selective oxidation of alcohols to aldehydes or ketones. Such salts can be generated catalytically from a nitroxide in the presence of a secondary oxidation procedure, either chemical or electrochemical,¹³³ or with two equivalents of acid and two equivalents of a nitroxide.¹³⁴ When **87** was mixed with acetylenic alcohol **88** in dichloromethane, aldehyde **89** was isolated in 93% yield.¹³⁵ The reaction is readily monitored as the initial yellow slurry changes to a white slurry and the presence of unreacted oxidant can be checked with starch.¹³⁵ It is not necessary to use anhydrous conditions, and it was discovered that the rate of reaction was enhanced by the presence of silica gel. This reagent is compatible for the mild oxidation of many alcohols, including aliphatic primary and secondary as well as allylic and benzylic alcohols, although nitrogen-containing compounds are sometimes problematic unless pyridine is added to the reaction. Note that the stable free radical TEMPO (**91**) also oxidizes alcohols in the presence of an acid catalyst. An example is the conversion of collectodiol (**90**) to grahamimycin A (**92**), in 76% yield in a synthesis reported by O'Doherty and Hunter.¹³⁶

^{130.} Evans, D.A.; Sheppard, G.S. J. Org. Chem. 1990, 55, 5192.

^{131.} Paquette, L.A.; Chang, S.-K. Org. Lett. 2005, 7, 3111.

 ^{132. (}a) Bobbitt, J.M.; Flores, M.C.L. *Heterocycles* 1988, 27, 509. Also see, (b) Golubev, V.A.; Zhdanov, R.I.; Gida, V.M.; Rozantsev, É.G. Bull. Acad. Sci. USSR, Chem. Sci. 1971, 20, 768; (c) Golubev, V.A.; Miklyush, R.V. Russ. J. Org. Chem. 1972, 8, 1376.

^{133. (}a) de Nooy, A.E.J.; Besemer, A.C.; van Bekkum, H. Synthesis 1996, 1153; (b) Anelli, P.L.; Montanari, F.; Quici, S. Org. Synth. Coll. Vol. VIII 1993, p 367.

^{134.} Ma, Z.; Bobbitt, J.M. J. Org. Chem. 1991, 56, 6110.

^{135.} Bobbitt, J.M. J. Org. Chem. 1998, 63, 9367.

^{136.} Hunter, T.J.; O'Doherty, G.A. Org. Lett, 2002, 4, 4447.



3.2.F. Alternative Metal Compounds As Useful Oxidizing Agents

The oxidation of alcohols is not limited to chromium derivatives, DMSO derivatives, or hypervalent iodine compounds. There are several metal-based reagents that are very effective, particularly with sensitive functionality. This section will examine several of the more important reagents.

3.2.F.i. Tetrapropylammonium Perruthenate-Ley Oxidation. Ruthenium derivatives have been used for oxidation reactions. A particularly useful one is tetrapropylammonium perruthenate (TPAP), introduced by Ley for the oxidation of alcohols and now called Ley oxidation.¹³⁷ It is a very mild oxidizing agent that is compatible with many sensitive functional groups. In a synthesis of (–)-cylindricine C, for example, Hsung and co-workers oxidized the secondary alcohol unit in **93** with TPAP to give an excellent yield of ketone **94**, without disturbing the α -chloro group.¹³⁸



3.2.F.ii. Oppenauer Oxidation. In oxidation reactions involving both Cr(VI) and DMSO reagents, the alcohol is converted to a complex and the α -hydrogen of an alcohol removed as an acid. A classical and alternative method for the oxidation of alcohols focuses on the reversible

⁽a) Griffith, W.P.; Ley, S.V.; Whitcombe, G.P.; White, A.D. J. Chem. Soc. Chem. Commun. 1987, 1625;
(b) Griffith, W.P.; Ley, S.V. Aldrichimica Acta 1990, 23, 13-19;
(c) Ley, S.V.; Norman, J.; Griffith, W.P.; Marsden, S.P. Synthesis 1994, 639.

^{138.} Swidorski, J.J.; Wang, J.; Hsung, R.P. Org. Lett. 2006, 8, 777.

reaction between ketones and metal alkoxides, which is especially effective when the metal is aluminum¹³⁹ Reversibility in the aluminum alkoxide reaction was first demonstrated by Verley¹⁴⁰ and Ponndorf¹⁴¹ for the reaction of a ketone with an aluminum alkoxide, which led to formation of a new aluminum alkoxide and a new ketone. Oppenauer oxidized unsaturated steroidal alcohols using aluminum triisopropoxide [Al(O*i*-Pr)₃] in acetone, in 1937.¹⁴² The acetone acts as a hydrogen acceptor, and the presence of excess acetone drives the reaction toward the oxidation product. Oppenauer used this method to oxidize the alcohol unit of Δ^5 -3hydroxy steroids such as **95** to the Δ^4 -3 ketone (**96**).¹⁴² The observed shift of the double bond into conjugation is very common when the alkene moiety is in close proximity to the reactive center. This reaction has been applied to many steroids and simple alcohols, and has come to be called **Oppenauer oxidation**.^{139,143} An uncatalyzed version of this reaction was reported to proceed in supercritical fluids.¹⁴⁴ Note that this reaction is the reverse of the **Meerwein-Ponndorf-Verley reduction**¹⁴⁵ (see section 4.9.I).



The reaction proceeds via an aluminum coordination complex (97), with transfer of a hydrogen atom from one alkoxy carbon to another to give 100.^{139,146} Since 97 is a Lewis acid it reacts with the available Lewis base (the carbonyl oxygen of the ketone) to form an ate complex (98), and this is followed by transfer of H_a from the alkoxide carbon of 98 to the alkoxy unit from the ketone carbon (giving 99) via a six-center transition state. Transfer of H_a between 98 and 99 is a reversible process. Just as 97 and 98 are in equilibrium, so the new *ate* complex 99 is in equilibrium with a new alkoxide (100) and a new ketone. If an excess of the original ketone (RCOR₁) is added, the equilibrium is shifted toward 100, and the new ketone (R₂COR₃). The original ketone (RCOR₁) acts as a hydrogen acceptor in this process. If the goal is oxidation of an alcohol, acetone is the solvent and aluminum triisopropoxide is the reagent. In the previously cited example, oxidation of secondary alcohol 95 in acetone gave ketone 96.

- 139. Djerassi, C. Org. React. 1951, 6, 207.
- 140. Verley, A. Bull. Chim. Soc. Fr. 1925, 37, 537.
- 141. Ponndorf, W. Angew. Chem. 1926, 39, 138.
- 142. Oppenauer, R.V. Rec. Trav. Chim. 1937, 56, 137.
- 143. (a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, *2006*, p ONR-68; (b) de Graauw, C.F.; Peters, J.A.; van Bekkum, H.; Huskens, J. *Synthesis 1994*, 1007.
- 144. Sominsky, L.; Rozental, E.; Gottlieb, H.; Gedanken, A.; Hoz, S. J. Org. Chem. 2004, 69, 1492.
- 145. The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-59.
- 146. (a) Woodward, R.B.; Wendler, N.L.; Brutschy, F.J. J. Am. Chem. Soc. 1945, 67, 1425; (b) Lutz, R.E.; Gillespie, Jr., J.S. Ibid. 1950, 72, 344; (c) Von E. Doering, W.; Young, R.W. Ibid; 1950, 72, 631.

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Oppenauer oxidation of saturated alcohols is often sluggish, but this problem can be overcome by changing the structure of the metal alcoholate, the hydrogen acceptor or by changing the solvent. Aluminum tri-*tert*-butoxide, triisopropoxide, or tri-*n*-propoxide are the most commonly used alkoxides, but aluminum triphenoxide gave better yields with saturated hydroxy steroids.¹⁴⁷ Acetone (often with benzene as a co-solvent) is the most commonly used hydrogen acceptor, although cyclohexanone in a solution of toluene or xylene is also used. The latter conditions allow higher reaction temperatures and shorter reaction times.⁹⁷ Ideally, the ketone that serves as the hydrogen acceptor should have a high reduction potential (sec. 3.1), but a large excess of the ketone can compensate for a low reduction potential, as with acetone.¹⁴⁸ Benzophenone is used occasionally because it is resistant to condensation reactions (Chaps. 8 and 9) that can compete.

Nonsteroidal alcohols can be oxidized by this method,^{149,150} but Oppenauer oxidation of primary alcohols tends to give a low yield of the aldehyde. Although oxidation of benzyl alcohol gave about 60% of benzaldehyde, geraniol (**101**) gave only 35% of geranial (**102**).¹⁵¹ Schinz and co-workers found that aldehydes are effective hydrogen acceptors when used for the oxidation of primary alcohols to aldehydes. If the boiling point of that aldehyde was \geq 50°C *higher* than the expected product, the aldehyde product could be distilled as it was formed.^{152,151b}



Two common side reactions were mentioned previously. One is migration of a nonconjugated double bond into conjugation, and the other is condensation of the aldehyde product with the

- 149. (a) Reference 139, p 211; (b) Ungnade, H.E.; Ludutsky, A. J. Am. Chem. Soc. 1947, 69, 2629.
- 150. (a) Reference 139, p 219; (b) Adams, R.; Hamlin, Jr., K.E. J. Am. Chem. Soc. 1942, 64, 2597.
- (a) Yamashita, M.; Matsumura, R. J. Chem. Soc. Jpn. 1943, 64, 506 [Chem. Abstr. 41: 3753g 1947]; (b) Reference 139, p 222.
- (a) Schinz, H.; Lauchenauer, A.; Jeger, O.; Rüegg, R. Helv. Chim. Acta 1948, 31, 2235; (b) Rüegg, R.; Jeger, O. Ibid. 1948, 31, 1753; (c) Lauchenauer, A.; Schinz, H. Ibid. 1949, 32, 1265.

 ^{147. (}a) Reference 139, p 226; (b) Reich, H.; Reichstein, T. Arch. Inter. Pharmacodynamie 1941, 65, 415; [Chem. Abstr. 35: 55262 1941].

^{148. (}a) Adkins, H.; Cox, F.W. J. Am. Chem. Soc. 1938, 60, 1151; (b) Cox, F.W.; Adkins, H. Ibid. 1939, 61, 3364; (c) Baker, R.H.; Adkins, H. Ibid. 1940, 62, 3305; (d) Adkins, H.; Elofson, R.M.; Rossow, A.G.; Robinson, C.C. Ibid. 1949, 71, 3622.

carbonyl hydrogen acceptor (this is an acid catalyzed **aldol condensation**, sec. 9.4.A). In recent years, metal catalysts other than aluminum have diminished the occurrence of these side reactions, although other aluminum catalysts have also been developed. Maruoka, for example, reported that the modified aluminum catalyst **103** was highly effective for Oppenauer oxidation of alcohols under mild conditions.¹⁵³ An example of an alternative



metal catalyst is the cyclopentadienyl zirconium reagent (Cp₂ZrH₂) developed by Ishii et al.¹⁵⁴ that was shown to be an effective catalyst in the Oppenauer oxidation using a 1:1 ratio of alcohol to hydrogen acceptor. The use of this catalyst led to excellent yields of aldehydes from primary alcohols, but heating in an autoclave without solvent was required despite being catalytic in the zirconium reagent. Geraniol (**101**) was oxidized to geranial (**102**) in 92% yield by this method, using benzophenone as the hydrogen acceptor. Magnesium-catalyzed Oppenauer oxidations have been observed in Grignard alkylation reactions with aldehydes (sec. 8.4.C), where direct oxidation of the magnesium alkoxide generated during the reaction prior to hydrolysis is possible.¹⁵⁵

3.2.F.iii. Oxidation with Manganese Dioxide. Although manganese dioxide (MnO_2) is a common form of Mn(IV), it is rather insoluble in most organic solvents. Manganese dioxide is the usual end-product of permanganate oxidations in basic solution (sec. 3.5.A). The reduction potential of MnO_2 is 1.208 volts for the following reaction.¹⁷

$$MnO_2 + 4 H^+ + 2 e^- \rightarrow Mn^{2+} + 2 H_2O$$
 1.208 V

Manganese dioxide is capable of oxidizing alcohols to ketones or aldehydes, and the reaction proceeds via a radical intermediate (see below), producing MnO (which is Mn²⁺) as the by-product. Manganese dioxide oxidizes primary and secondary alcohols to the aldehyde or ketone, respectively, in neutral media.¹⁵⁶ Ball, et al discovered this reaction, by precipitating manganese dioxide and then converting vitamin A (**104**) to retinal (**105**) in 80% yield.¹⁵⁷



There are several ways to prepare this reagent, and its oxidizing power is strongly influenced by the method of preparation.¹⁵⁶ One of the more common methods involves precipitation of MnO_2 from a warm aqueous solution of $MnSO_4$ and $KMnO_4$ at a particular pH. The precipitated

^{153.} Ooi, T.; Otsuka, H.; Miuraa, T.; Ichikawa, H.; Maruoka, K. Org. Lett. 2002, 4, 2669.

^{154.} Ishii, Y.; Nakano, T.; Inada, A.; Kishigami, Y.; Sakurai, K.; Ogawa, M. J. Org. Chem. 1986, 51, 240.

^{155.} Byrne, B.; Karras, M. Tetrahedron Lett. 1987, 28, 769.

^{156. (}a) Fatiadi, A.J. Synthesis 1976, 65, 133; (b) Evans, R.M. Quart. Rev. Chem. Soc. (London) 1959, 13, 61.

^{157.} Ball, S.; Goodwin, T.W.; Morton, R.A. Biochem. J. 1948, 42, 516.

reagent is then activated by heating to 100-200°C or higher¹⁵⁸ for several hours. The solvent used for the oxidation is important, since the reaction proceeds by coordination of both substrate and reagent to the MnO₂. The solvent can influence the degree of adsorption and desorption of the alcohol on the manganese dioxide. If a primary or secondary alcohol is used as the solvent, competition for adsorption sites with the alcohol will diminish the yield of oxidation products. Many other solvents can been used, including alkanes (petroleum ether, cyclopentane), chlorinated hydrocarbons (CH₂Cl₂, CHCl₃), ethers (diethyl ether, THF), acetone, acetonitrile, DMSO, DMF, and pyridine. Reaction times range from a few minutes for allylic alcohols to several hours for saturated alcohols. The oxidation of **104** required six days, an indication that activating the manganese dioxide prior to addition of organic substrate is important.

Both Goldman¹⁵⁹ and Henbest et al.¹⁶⁰ proposed a radical intermediate in oxidations using manganese dioxide. Goldman's mechanism is shown for reaction with benzyl alcohol, and it involves adsorption of the alcohol on manganese dioxide (see **106**), followed by formation of a coordination complex (**107**). Coordination in this manner allows electron transfer, which generates a radical (**108**) in a process that is accompanied by reduction of Mn(IV) to Mn(III). A second electron transfer generates the carbonyl product adsorbed on Mn(OH)₂ as in **109**. The product is desorbed, with loss of water, to complete the oxidation. Hall and Story proposed an alternative ionic mechanism for oxidation, which invoked formation of a manganate ester.¹⁶¹



[Reprinted with permission from Goldman, I.M. J. Org. Chem. 1969, 34, 3289. Copyright © 1969 American Chemical Society.]

Manganese dioxide is probably most useful for the oxidation of allylic and benzylic alcohols. In a synthesis of sordaricin,¹⁶² Mander and Thomson oxidized the allylic alcohol unit in **110** to conjugated aldehyde **111** in >86% yield using manganese dioxide. Oxidation of alcohols by manganese dioxide is influenced by the steric encumbrance around the carbon bearing the hydroxyl moiety. In general, there is no significant difference in the rate of oxidation of cis- and trans- isomeric alkenes, and there appears to be little or no cis/trans isomerization during the oxidation. Reaction of *cis*- or *trans*-2-methyl-2-penten-1-ol with MnO₂ led to either the cis- or

^{158.} Pratt, E.F.; Van de Castle, J.F. J. Org. Chem. 1961, 26, 2973.

^{159.} Goldman, I.M. J. Org. Chem. 1969, 34, 3289.

^{160.} Henbest, H.B.; Stratford, M.J.W. Chem. Ind. (London) 1961, 1170.

^{161.} Hall, T.K.; Story, P.R. J. Am. Chem. Soc. 1967, 89, 6759.

^{162.} Mander, L.N.; Thomson, R.J. J. Org. Chem. 2005, 70, 1654

the trans-aldehyde in 64% or 83% yield, respectively.¹⁶³ Boehm et al. noted, however, that some cis-trans isomerization occurred in similar oxidation of pentadienols and pentenynols.¹⁶⁴



Manganese dioxide oxidizes allylic and benzylic alcohols faster than primary saturated alcohols, but primary and secondary allylic alcohols react at about the same rate.¹⁶⁵ Oxidation of a secondary benzylic alcohol is faster than a primary saturated alcohol. The secondary benzylic alcohol group in **112** was oxidized to give aryl ketone **113** (94% yield), for example, rather than the primary aliphatic hydroxyl.¹⁶⁶



Although the oxidation of allylic and benzylic alcohols is faster, saturated alcohols do react with manganese dioxide. Their oxidation requires a neutral medium, freshly prepared and activated manganese dioxide, the proper solvent and long reaction times. Simple examples are the oxidation of 2-propanol to acetone and 2-methyl-1-propanol to 2-methyl-propanal, both in 50% yield.¹⁶⁷ The conditions are not too vigorous, however, and complex molecules are easily oxidized with manganese dioxide. Even saturated secondary alcohols, which are relatively unreactive,¹⁶⁷ can be oxidized if no allylic or benzylic alcohols are present elsewhere in the molecule.¹⁶⁸ There is little difference in rate between secondary allylic alcohols and primary saturated alcohols, but steric and/or conjugative effects may have an influence on the reaction. Primary allylic and secondary allylic alcohols are often oxidized with essentially the same rate of reaction, leading to poor selectivity.¹⁶⁹ If a large excess of MnO₂ is used, it is possible to

- 167. Barakat, M.Z.; Abdel-Wahab, M.F.; El-Sadr, M.M. J. Chem. Soc. 1956, 4685.
- 168. Wada, K.; Enomoto, Y.; Matsui, K.; Munakata, K. Tetrahedron Lett. 1968, 4673.
- 169. Kienzle, F.; Mayer, H.; Minder, R.E.; Thommen, W. Helv. Chim. Acta 1978, 61, 2616.

^{163.} Chan, K.C.; Jewel, R.A.; Nutting, W.H.; Rapoport, H. J. Org. Chem. 1968, 33, 3382.

^{164. (}a) Boehm, E.E.; Thaller, V.; Whiting, M.C. J. Chem. Soc. 1963, 2535; (b) Boehm, E.E.; Whiting, M.C. Ibid. 1963, 2541.

^{165.} For a synthetic example involving primary allylic vs. primary saturated alcohols, see Graham, S.H.; Jonas, D.A. *J. Chem. Soc. C* **1969**, 188.

 ^{166. (}a) Adler, E.; Becker, H.D. *Acta Chem. Scand.* 1961, 15, 849; (b) for a related reaction, see Freudenberg, K.; Lehmann, B. *Chem. Ber.* 1960, 93, 1354.

oxidize more than one alcoholic position without affecting other labile functionality.¹⁷⁰

Allylic alcohols can react with MnO₂ under certain conditions to give the conjugated acid or ester (in alcoholic solvents). In an example taken from Weinreb and co-worker's synthesis of cylindrospermopsin, allylic alcohol **114** was treated with MnO₂ in the presence of NaCN and methanol to give a 62% yield of methyl ester **115**.¹⁷¹



The purpose of cyanide in this oxidation is to convert the conjugated aldehyde to a conjugated ester. In a related reaction using HCN, Corey and co-workers¹⁷² showed that reaction of a conjugated aldehyde with HCN/CN⁻ generates a cyanohydrin such as **116**. Subsequent oxidation with MnO₂ gave cyanoketone, **117**, which reacted with the alcoholic solvent (methanol) to give the corresponding methyl ester.



The functional group transforms available from reactions of MnO₂ are

$$\underset{R}{\overset{R}{\models}} \circ \underset{R}{\overset{R}{\longrightarrow}} \overset{R}{\underset{R}{\rightarrow}} \circ \underset{R}{\overset{R}{\longrightarrow}} \overset{OH}{\underset{R}{\rightarrow}} \overset{R}{\underset{R}{\rightarrow}} \overset{CO_2R}{\underset{R}{\xrightarrow}} \overset{R}{\underset{R}{\rightarrow}} \overset{CHO}{\underset{R}{\rightarrow}} \overset{CHO}{\underset{R}{\rightarrow}} \overset{R}{\underset{R}{\rightarrow}} \overset{R}{\underset{R}{\rightarrow}} \overset{CHO}{\underset{R}{\rightarrow}} \overset{R}{\underset{R}{\rightarrow}} \overset{R}{\underset{R}{\rightarrow}} \overset{CHO}{\underset{R}{\rightarrow}} \overset{R}{\underset{R}{\rightarrow}} \overset{R}{\underset{R}{} \overset{R}{\underset{R}{\rightarrow}} \overset{R}{\underset{R}{}} \overset{R}{\underset{R}{}} \overset{R}{\underset{R}{}} \overset{R}{\underset{R}{}} \overset{R}{\underset{R}{}} \overset{R}{\underset{R}{}} \overset{R}{} \overset{R}$$

3.2.G. Oxidations with Silver (Silver Carbonate and Silver Oxide)

Silver ion is an excellent oxidizing agent. The reduction potentials for several silver reagents rank them among the more potent of reagents. The most common reagents are silver carbonate (Ag₂CO₃, reduction potential = 0.4769 V), silver(I) oxide (Ag₂O, reduction potential = 0.342 V), and silver(II) oxide (AgO, reduction potential = 0.599 V), where the reduction potentials are taken from the following reactions:¹⁷

 ⁽a) Meinwald, J.; Opheim, K.; Eisner, T. *Tetrahedron Lett.* 1973, 281; (b) Miller, C.H.; Katzenellenbogen, J.A.; Bowlus, S.B. *Ibid.* 1973, 285.

^{171.} Heintzelman, G.R.; Fang, W.-K.; Keen, S.P.; Walalce, G.A.; Weinreb, S.M.J. Am. Chem. Soc. 2002, 124, 3939.

^{172.} Corey, E.J.; Gilman, N.W.; Ganem, B.E. J. Am. Chem. Soc. 1968, 90, 5616.

$$Ag_2CO_3 + 2e^- \rightarrow 2Ag + CO_3^{2-}$$
 0.4769 V

 $Ag_2O + H_2O + 2e^- \rightarrow 2Ag + 2OH^- \qquad 0.342V$

 $2 \text{ AgO} + \text{H}_2\text{O} + 2 \text{ e}^- \rightarrow \text{Ag}_2\text{O} + 2 \text{ OH}^-$ 0.599 V

3.2.G.i. Silver Carbonate. Silver carbonate (Ag₂CO₃) is not a powerful oxidizing agent but it is useful in Organic chemistry. Rapoport et al. were probably the first to use silver carbonate for the oxidation of alcohols to carbonyl derivatives. Rapoport refluxed codeine (**118**) with silver carbonate in benzene and obtained a 75% yield of codeinone (**119**).¹⁷³ In later work King et al. oxidized codeine with silver carbonate in refluxing toluene or xylene and obtained an 85% yield of **119** with a much shorter reaction time.¹⁷⁴



Fétizon, et al. modified the reagent by condensing silver carbonate on Celite. It was found that reaction of primary alcohols with excess silver carbonate on Celite gave excellent yields of the corresponding aldehyde, illustrated by the conversion of geraniol (see **101** above) to geranial (**102**) in 97% yield, using four equivalents of Ag₂CO₃ on Celite, in refluxing benzene.¹⁷⁵ This modified reagent is now known as **Fétizon's reagent**.¹⁷⁶ Saturated primary alcohols are converted to aldehydes in excellent yields and, as seen with Rapoport's work, secondary alcohols are also oxidized to ketones.

Fétizon proposed a mechanism by which adsorption of the alcohol on silver carbonate gave a species such as **120**. One-electron transfer via the silver ion in **121** liberated the protonated carbonyl and carbonic acid (see **122**), which decomposed to carbon dioxide and water.¹⁷⁷ This mechanism involved four distinct processes:¹⁷⁸

- 174. King, W.; Penprase, W.G.; Kloetzel, M.C. J. Org. Chem. 1961, 26, 3558.
- 175. Fétizon, M.; Golfier, M. C.R. Acad. Sci. Ser. C 1968, 267, 900.
- 176. Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, *2005*, p. 778.
- 177. Fétizon, M.; Golfier, M.; Morgues, P. Tetrahedron Lett. 1972, 4445.
- 178. Kakis, F.J.; Fétizon, M.; Douchkine, N.; Golfier, M.; Mourgues, P.; Prange, T. J. Org. Chem. 1974, 39, 523.

^{173.} Rapoport, H.; Reist, H.N. J. Am. Chem. Soc. 1955, 77, 490.



- **1.** Reversible adsorption of alcohol on the surface of the oxidizing medium with the electron of oxygen forming a coordinated covalent bond with the silver ions.
- **2.** Oxidation of the C-H bond so the HCOH group is *coplanar* and *perpendicular* to the silver carbonate/Celite surface.
- **3.** A concerted irreversible homolytic shift of electrons to generate reduced silver atoms, hydrogen ions, and a protonated carbonyl.
- 4. Collapse to products with carbonate ion acting as a hydrogen ion acceptor, generating carbonic acid, which decomposes to carbon dioxide and water.

Polar solvents inhibit the reaction, presumably by interfering with the adsorption process as noted in the mechanism proposed for manganese dioxide oxidations. Oxidation of 1-heptanol to heptanal with Fétizon's reagent was quantitative when the solvent was 35% hexanes. When benzene was used as a solvent, the yield of heptanal was 90% but the yield was < 1% in ethyl acetate, methyl ethyl ketone, or acetonitrile.¹⁷⁸ Since the oxidation is a heterogeneous reaction requiring adsorption of the alcohol substrate, as the surface area of the reagent increases (increased by precipitation on Celite) the rate of oxidation increases. An optimum ratio is reached beyond which increasing the silver carbonate/Celite ratio slows the oxidation.¹⁷⁸

The reaction does not have carbocation intermediates and even optically pure 1,2,2triphenylethanol, which is known to have a strong tendency toward rearrangement,¹⁷⁹ undergoes oxidation without racemization or rearrangement.¹⁷⁸ The oxidation of hindered alcohols suffers because of steric hindrance, due to the requirement that the alcohol must be adsorbed on the surface of the reagent. All groups undergoing a bond change must be coplanar in the transition state and perpendicular to the plane of the solid surface. Any combination of steric and conformational factors that inhibit this transition state will slow the reaction. 5 α -Androstan-6 α -ol, for example, is extremely unreactive with silver carbonate. The diminished rate is attributed to the difficulty in adsorption to the silver, which is hindered by the C19 methyl and the C4 methylene group.¹⁷⁸ This contrasts sharply with 5 α -androstan-6 β -ol, which is not sterically impeded and undergoes rapid oxidation. The accessibility of the hydrogen attached to the carbon bearing the hydroxyl group is also important. *endo*-2-Norbornanol is

 ⁽a) Collins, C.J.; Bonner, W.A.; Lester, C.T. J. Am. Chem. Soc. 1959, 81, 466; (b) Bonner, W.A.; Collins, C.J. Ibid. 1953, 75, 5372, 5379; (c) Collins, C.J.; Bonner, W.A. Ibid. 1955, 77, 92, 99, 6725; (d) Bonner, W.A.; Collins, C.J. Ibid. 1956, 78, 5587.

oxidized about 50 times faster than exo-2-norbornanol, for example.¹⁸⁰

It is possible to produce a controlled over-oxidation reaction with silver carbonate. Fétizon discovered that 1,3- and 1,4-diols are smoothly oxidized to butyrolactone and valerolactone derivatives in good yield.¹⁸¹ Oxidation of a diol can be accomplished in the presence of a variety of functional groups, even another alcohol, and a primary alcohol is oxidized faster than a secondary alcohol.¹⁸²a An example of lactone formation is the conversion of 1,4-diol **123** to lactone **124** in Inoue and co-worker's synthesis of an unnatural enantiomer of merrilactone A.^{182b}



The functional group transforms for silver carbonate are



3.2.G.ii. Silver(I) Oxide. Silver(I) oxide (Ag₂O) is the weakest of the silver oxidizing agents introduced in this section. It is used primarily for the selective oxidation of aldehydes to carboxylic acids. One might expect that the oxidation of an aldehyde to a carboxylic acid is facile, but there are cases where the substrate bearing the aldehyde moiety is also susceptible to oxidation. In such cases, a mild and selective oxidant is required and Ag(I) oxide is often the reagent of choice. Silver(I) oxide was used by Rizzacasa and co-workers in the oxidation of **125** to carboxylic acid **126** in a synthesis of (–)-cinatrin B.¹⁸³ Oxidation of the alcohol unit



^{180.} Reference 178, see citation 17 therein, Eckert-Maksic, M.; Tusek, L.; Sunko, D.E. *Croat. Chem. Acta* 1971, 43, 79. [*Chem. Abstr.* 75: 4999d 1971].

183. Cuzzupe, A.N.; Di Florio, R.; Rizzacasa, M.A. J. Org. Chem. 2002, 67, 4392.

^{181. (}a) Fétizon, M.; Golfiere, M.; Louis, J.-M. J. Chem. Soc. Chem. Commu1969, 1118, 1102; (b) Fétizon, M.; Golfier, M.; Louis, J.-M. Tetrahedron 1975, 31, 171.

 ⁽a) Chandrasekhar, M.; Chandra, K.L.; Singh, V.K. J. Org. Chem. 2003, 68, 4039 for a synthesis of (+)-boronolide; (b) Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama, M.; Moriyama, M.; Fukuyama, Y.J. Org. Chem. 2007, 72, 3065.

in 125 with the **Dess-Martin reagent** (see sec. 3.2.D) gave an aldehyde that was oxidized *in* situ with silver oxide. The silver oxide reagent was prepared in situ by mixing a solution of silver nitrate (AgNO₃) and excess KOH.^{184,185} In a synthesis of strigol, Pepperman examined the oxidation of 127 to keto aldehyde 128,¹⁸⁶ with the goal of converting 128 to 129. Several oxidizing agents were used (see Table 3.2),¹⁸⁶ all converting the secondary alcohol unit in 127 to the ketone. Further oxidation to acid **129** was a problem because of extensive decomposition that lowered the yield. However, oxidation of **128** followed by treatment with silver (I) oxide gave 129 in good yield with few by-products. Despite the good yield of 129 eventually obtained in Table 3.2, oxidation of an α , β -unsaturated aldehyde usually gives a poor yield of the acid. Oxidation of **128** had previously given a maximum of 40% yield of **129**.¹⁸⁷ Frank¹⁸⁸ found that oxidation of β -cyclocitral gave only 23% conversion to β -cyclogeranic acid with silver oxide. In 128, the extended π configuration seemed to facilitate oxidation under the conditions used and it behaves differently than conjugated aldehydes. The oxidation of saturated aldehydes is straightforward.¹⁸⁹ Silver oxide can also oxidize primary alcohols directly to the acid (e.g., 1-dodecanol to dodecanoic acid).¹⁹⁰ Cleavage to the diacid accompanies oxidation of 1,2-diols (sec. 3.7.C), as in the conversion of 1,2-cyclohexanediol to adipic acid in 89% yield.¹⁹⁰

Me Me CHO OH 127	→ Me Me CHO 0 128	$\rightarrow \bigvee_{\substack{\text{O}\\0\\129}}^{\text{Me}} \bigoplus_{\substack{\text{CO}_2\text{H}\\0\\129}}^{\text{Me}}$			
<u>Reagent</u>		<u>% 129</u> ^a			
KMnO ₄ •H ₂ SO ₄		13.5			
air (bubbled)		37			
air (thin film)		46			
Ag ₂ O		72			
MnO ₂ •NaCN		80 (as Me ester)			
Jones		55			
^a Based on keto-aldehyde 128					
[Reprinted with permission from Pepperman, A.B. J. Org. Chem. 1981, 46, 5039. Copyright © 1981 American Chemical Society.]					

 Table 3.2. Oxidation of 128 to Keto Acid 129

The functional group transforms available to silver (I) oxide are

- 184. Campaigne, E.; LeSuer, W.M. Org. Synth. Coll. Vol. 4 1963, 919.
- 185. Pearl, I.A. Org. Synth. Coll. Vol. 4 1963, 972.
- 186. Pepperman, A.B. J. Org. Chem. 1981, 46, 5039.
- 187. Thomason, S.C.; Kubler, D.G. J. Chem. Educ. 1968, 45, 546.
- 188. Frank, A.W. J. Heterocyclic Chem. 1981, 18, 549.
- 189. For a synthetic example, see Kuroda, C.; Theramongkol, P.; Engebrecht, J.R.; White, J.D. J. Org. Chem. 1986, 51, 956.
- 190. Kubias, J. Collect. Czech. Chem. Commun. 1966, 31, 1666.



3.2.G.iii. Silver(II) Oxide. Silver(II) oxide (AgO) is the most powerful of the three oxidants presented in this section. Although it is not widely used, Ag(II) oxide converts aldehydes and alcohols to carboxylic acids or ketones.¹⁹¹ The reagent can be prepared by oxidation of silver nitrate with potassium peroxydisulfate ($K_2S_2O_8$) in an alcoholic solvent.¹⁹² Benzyl alcohol was oxidized to benzaldehyde in aqueous solutions of AgO,^{192a} and in neutral or alkaline solution further oxidation gave benzoic acid in 57% yield.^{192b} Corey found that a mixture of AgO and sodium cyanide converted aldehydes such as 130 to the acid (**131**) in 97% yield, without isomerization of the double bond into conjugation.¹⁷² Oxidation with manganese dioxide and sodium cyanide in acetic acid gave the ethyl ester.¹⁷² Corey observed that cinnamaldehyde gave little or no oxidation, but oxidation of **128** with this reagent gave 80% of **129**.



3.2.H. Other Transition Metal Oxidants

This section contains several oxidizing reagents that do not easily fall into a single category. The intent is to show some of the variety in reagents that convert alcohols to ketones and aldehydes. These reagents are not as widely used as the reagents presented above. The main purpose is to show that alternative reagents (sometimes they are exotic) are currently available or in development that may solve a difficult oxidation problem. The reader is encouraged to conduct a thorough search of the literature since several alternative reagents will probably be found that may solve a given synthetic problem. Most of these alternative reagents use transition metal derivatives.

It is known that potassium permanganate can over-oxidize primary alcohols to the corresponding carboxylic acid, and secondary alcohols can undergo oxidative cleavage. This oxidizing power can be moderated by complexing permanganate ion with another cationic species. Trimethylcetylammonium permanganate,¹⁹³ bis(bipyridylcopper) permanganate (bpy₂CuMnO₄)¹⁹⁴ and *n*-butyl permanganate¹⁹⁵ have all been used in the oxidation of alcohols.

- 193. Rathore, R.; Bhushan, V.; Chandrasekaran, S. Chem. Lett. 1984, 2131.
- 194. Firouzabadi, H.; Sardarian, A.R.; Naderi, M.; Vessal, B. Tetrahedron 1984, 40, 5001.
- 195. Firouzabadi, H.; Mostafavipoor, Z. Bull. Chem. Soc. Jpn. 1983, 56, 914.

 ⁽a) Syper, L. *Tetrahedron Lett.* 1967, 4193; (b) Clarke, T.G.; Hampson, N.A.; Lee, J.B.; Morley, J.R.; Scanlon, B. *Ibid.* 1968, 5685.

 ⁽a) Hammer, R.N.; Klemberg, J. Inorg. Synth. 1953, 4, 12; (b) Fieser, L.; Fieser, L. Reagents For Organic Synthesis, Vol. 2, Wiley, New York, 1969, p 369.
Molybdenum reagents have been used for oxidations, and there are many variations in the useful ligands, including: $(NH_4)_6Mo_7O_{24} \cdot 2 H_2O$, ^{196,197} Mo(CO)₆ · Py-cetyl, ^{198,199} Mo(N₂)₂(dpe)₂, ²⁰⁰ and BnNMe₃⁺ OMoBr₄^{-.201} Many of these reagents have been shown to be selective for the oxidation of secondary alcohols, as in the oxidation of 1,10-undecanediol (**132**) to keto alcohol, **133**.¹⁹⁶

Cerium(IV) has been used extensively,²⁰² and the two most common reagents are probably ceric ammonium sulfate $[Ce(SO_4)_2 \cdot 2(NH_4)_2SO_4 \cdot 2 H_2O]$ and ceric ammonium nitrate $[Ce(NH_4)_2(NO_3)_6]$.²⁰³ Firouzabadi et al. have used modified cerium reagents such as $Ce(OH)_3O_2H^{204}$ and $[(NO_3)_3Ce]_3H_2IO_6^{205}$ for the oxidation of primary alcohols, especially benzylic and allylic alcohols.



3.3. FORMATION OF PHENOLS AND QUINONES

In addition to the oxidation of aliphatic hydroxy compounds, aromatic derivatives that contain hydroxyl groups (phenol derivatives) can also be oxidized.²⁰⁶ The course of the oxidation disrupts the aromatic ring to give quinones, which are important components in a variety of natural products.²⁰⁷ It is also possible to convert aromatic hydrocarbons to phenols by oxidation. Quinones are obtained by oxidation of phenols and a phenol can be very loosely viewed as an enol. Inclusion of this chemistry immediately after discussing the oxidation of alcohols to ketones, aldehydes, or acids is done with the goal of providing some continuity in studying the oxidation of hydroxyl compounds.

^{196.} Trost, B.M.; Masuyama, Y. Tetrahedron Lett. 1984, 25, 173.

^{197.} Sur, B.; Adak, M.M.; Pathak, T.; Hazra, B.; Banerjee, A. Synthesis 1985, 652.

^{198.} Yamawaki, K.; Yoshida, T.; Suda, T.; Ishii, Y.; Ogawa, M. Synthesis 1986, 59.

^{199.} Yamawaki, K.; Yoshida, T.; Nishihara, H.; Ishii, Y.; Ogawa, M. Synth. Commun. 1986, 16, 537.

^{200.} Tatsumi, T.; Hashimoto, K.; Tominaga, H.; Mizuta, Y.; Hata, K.; Hidai, M.; Uchida, Y. J. Organomet. *Chem.* 1983, 252, 105.

^{201.} Masuyama, Y.; Takahashi, M.; Kurusu, Y. Tetrahedron Lett. 1984, 25, 4417.

Richardson, W.H. in Oxidation in Organic Chemistry, Part A, Wiberg, K.B. (Ed.), Academic Press, New York, 1965, pp 244-277

^{203.} Kanemoto, S.; Tomioka, H.; Oshima, K.; Nozaki, H. Bull. Chem. Soc. Jpn. 1986, 59, 105.

^{204.} Firouzabadi, H.; Iranpoor, N. Synth. Commun. 1984, 14, 875.

^{205.} Firouzabadi, H.; Iranpoor, N.; Hajipoor, G.; Toofan, J. Synth. Commun. 1984, 14, 1033.

^{206.} Reference 20, p 1234

^{207.} For a review of the synthesis of quinones, particularly those useful in synthesis, see Owton, W.M. J. Chem. Soc. Perkin Trans. 1 **1999**, 2409.

3.3.A. Quinones



The quinone structure is incorporated in many naturally occurring compounds, generically called *quinoids*. The most common are the 1,4-quinones (*p*-quinones, **134**) and the 1,2-quinones (*o*-quinones, **135**).²⁰⁸ Quinoids can be prepared by many methods, including oxidation of non-quinoid precursors, cyclization

methods, condensation methods, and annulation methods.²⁰⁹ This section will focus only on oxidation reactions, which constitute the only completely general methodology.²⁰⁹

Phenolic derivatives are readily oxidized to quinoids with **Fremy's salt** (potassium nitrosodisulphonate $[(KO_3S)_2NO^{\bullet}]^{209,210}$ Fremy²¹¹ prepared this reagent in 1845 as the disodium salt, but Raschig prepared the potassium salt, which was more effective and remains the reagent of choice.²¹² Acidic solutions are very unstable, and the salt also decomposes in aqueous solutions at pH greater than 10. The most common solvents are aqueous alcohol and aqueous acetone, and the reaction is usually buffered with phosphate or acetate. The reaction is rapid and may be monitored by disappearance of the purple color of the radical. Teuber and Rau proposed a simple mechanism for the oxidation of phenol.²¹³ Electron transfer from Fremy's salt to phenol generates a radical species (**136**), and this reacts with excess Fremy's salt to give an addition product, **137**. Loss of the hydrogen α to the oxygen moiety in **137** leads to formation of the quinone (**134**) and potassium aminodisulfonate [HN(SO₃K)₂].



Fremy's salt <u>sometimes</u> undergoes <u>violent</u>, <u>spontaneous decomposition</u> but this appears to be <u>due to the presence of catalytic amount of nitrite ion</u>.

^{208.} The Chemistry of the Quinoid Compounds, Parts 1 and 2, Patai, S. (Ed.), Wiley, New York, 1974.

^{209.} Thomson, R.H. in *The Chemistry of the Quinoid Compounds*, Part 1, Patai, S. (Ed.), Wiley, New York, 1974, pp 111-161.

^{210.} Zimmer, H.; Lankin, D.C.; Horgan, S.W. Chem. Rev. 1971, 71, 229.

^{211.} Fremy, E. Ann. Chim. Phys. 1845, 15, 408.

^{212.} Raschig, F. Schwefel und Stickstoff-Studien, Verlag-Chemie, Leipzig-Berlin, 1924 (from citation 2 in reference 210).

^{213. (}a) Reference 209, p 112; (b) Teuber, H.J.; Rau, W. Chem. Ber. 1953, 86, 1036.

The steric demands on the reaction sometimes lead to formation of the less hindered *p*-quinone as the major product, with low yields of the ortho-quinones. The yield of *o*-quinone can be low even when the para- position is blocked. When both the ortho- and para-positions are not sterically hindered, the *p*-quinoid is usually the major product. When X = H in **138**, oxidation follows *path a* to give the 1,4-quinone. Formation of **139** is consistent with para-attack, and loss of the X group will give **134**. When X in **138** is alkoxy (X = OR) or alkyl (X = R), however, *path b* is preferred. Since the para-position is blocked the ortho- intermediate (**140**) is formed, and loss of the bis(disulfonate) in the usual manner (see above) gives the 1,2-quinone **141**. When X = Cl in **139**, the chlorine is usually lost with formation of the 1,4-quinone.²⁰⁹



Two important factors that influence the oxidation. One is electronic stabilization of the incipient phenoxy radical, and the other is the steric requirement connected with formation of the cyclohexadiene intermediate. The presence of electron-withdrawing groups can cause the oxidation to fail, or at least lead to a poorer yield.^{209,210,214}

Oxidation of phenols with Fremy's salt can be applied to many phenolic derivatives, as in the synthesis of verapliquinone A by Moody and co-workers²¹⁵ in which oxidation of **142** gave 1,4-quinone **143** in 65% yield. Oxidation of phenols with Fremy's salt requires a buffered medium, since the salt is stable in only a limited pH range, as previously mentioned. Many *o*-quinones are unstable to acidic conditions, and may give other products if the pH exceeds 7. For example, oxidation of **144** gave **145** in 85% yield under standard conditions but in acid solution that product dimerizes completely.²¹⁶ When the phenyl ring of the phenol contains a *p*-chlorine^{209,217} or a *tert*-butyl group,²¹⁸ these groups can be eliminated from the intermediate, generating a quinone.^{217,218} Elimination of the amino moiety to give a quinoid can accompany oxidation of aniline derivatives by Fremy's salt. Oxidation of 3-ethoxy-5-methylaniline, for example, gave 3-ethoxy-5-methyl-1,4-benzoquinone in 93% yield.²¹⁹

^{214.} Maruyama, K.; Otsuki, T. Bull. Chem. Soc. Jpn. 1971, 44, 2873.

^{215.} Davis, C.J.; Hurst, T.E.; Jacob, A.M.; Moody, C.J. J. Org. Chem. 2005, 70, 4414.

^{216.} Teuber, H.J.; Thaler, G. Chem. Ber. 1958, 91, 2253.

^{217.} Teuber, H.J.; Thaler, G. Chem. Ber. 1959, 92, 667.

^{218.} Magnusson, R. Acta Chem. Scand. 1964, 18, 759.

^{219.} Teuber, H.J.; Hasselbach, M. Chem. Ber. 1959, 92, 674.



Table 3.3. Oxidation of 2,6-Xylenol (146)

MeMe[0] → HO 146	Me Me 147	Me OH + Me	Me Me Me 148	$Me \qquad Me \qquad$
<u>Reagent</u>	<u>% 147</u>	<u>% 148</u>	<u>% 149</u>	<u>% Polymer</u>
AgNO ₃ /K ₂ S ₂ O ₈	27	51	5	5
CuSO ₄ /Na ₂ S ₂ O ₈	1	47	27	15
Cu(III) ClO ₄		30		45
CuSO ₄ /NaOCl		17	26	60
CuSO ₄ /air stream		3	9	20
FeCl ₃		54	14	15
K ₃ Fe(CN) ₆ /NaOH		52		25
MnO ₂ /4M H ₂ SO ₄			16	50
MnO ₂		53		4
CuSO ₄ /H ₂ O ₂		33	9	40
FeSO ₄ /H ₂ O ₂		22	3	55
TiCl ₃ /H ₂ O ₂	9	20	51	5
TiCl ₄ /H ₂ O ₂		50	38	10
SeO_2/H_2O_2	4	0.2	0	
NaIO ₄	13	0.3	9	75
$NO(SO_3K)_2$	15	00	74	15

Many other oxidizing agents convert phenols to quinones, including Cr(VI), but in general most give lower yields of quinone and higher percentages of dimerized products. Chromic acid is an effective oxidant for the conversion of phenols to quinones only when a para- substituent such as halogen, hydroxyl, or amino is present. The yields are often poor,²²⁰ but not always.²²¹ Anodic oxidation of phenols to quinones²²² can be very efficient. Bacon and Izzat described the

^{220.} Reference 209, p 117.

^{221.} Conant, J.B.; Fieser, L.F. J. Am. Chem. Soc. 1923, 45, 2194.

^{222.} Reference 209, p 119.

oxidation of 2,6-xylenol (146) with a variety of oxidizing agents.²²³ In most cases, oxidation gave not only the expected quinone (149) but also dimerized products such as the coupled phenol (147) and the coupled quinone (148) as well as polymeric material.²²³ Table 3.3²²³ shows the product distribution obtained with different oxidizing agents. Clearly, Fremy's salt is the superior reagent in this list for preparation of quinone 149. It is also clear that the coupled quinone predominates with most oxidizing agents, and that polymerization is a problem. Table 3.3 shows the most common reagents used for the oxidation of phenols, including Fremy's salt, ferric ion, copper(II), titanium(III), and titanium(IV), as well as manganese dioxide,²²⁴ selenium dioxide, and sodium periodate.

Note that catechols (1,2-dihyroxybenzenes) are readily oxidized to *o*-quinones,²²⁵ but the products are often sensitive to any electrophilic or nucleophilic species in the reaction medium. Catechol itself gives **145**. Dimerization is as much a problem with catechols as with monophenols (see Table 3.3).²²⁶ The conversion of catechol to **145** used silver carbonate, and note that silver salts are the classical oxidation reagent for such transformations.²²⁷ Other reagent have been used to oxidize catechol derivatives, including ceric sulfate, lead tetraacetate, DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone),²²⁸ iodate, and periodate.²²⁹

There are many syntheses of molecules containing a quinone unit, and in most cases the quinone is oxidized late in the synthesis from a resorcinol or catechol derivative. In one example, taken from a synthesis of bisbolene by Vyvyan and co-workers²³⁰ oxidation of **150** with ceric ammonium nitrate gave an 83% yield of quinone **151**. As mentioned above, quinones can be formed from alkoxy derivatives of resorcinol or catechol, as well as from the parent hydroxyl compounds. In a synthesis of shikonin,²³¹ Couladouros and co-workers treated the *O*-silyl protected derivative **152** with ceric ammonium nitrate (CAN) and obtained a 92% yield of quinone **153**.



- 223. Bacon, R.G.R.; Izzat, A.R. J. Chem. Soc. C, 1966, 791.
- 224. Fatiadi, A.J. Synthesis 1976, 133.

- 226. (a) Harley-Mason, J.; Laird, A.H. J. Chem. Soc. 1958, 1718; (b) Horner, L.; Dürkheimer, W. Chem. Ber. 1958, 91, 2532.
- 227. (a) Balogh, V.; Fétizon, M.; Golfier, M. J. Org. Chem. 1971, 36, 1339; (b) Cason, J. Org. React. 1948, 4, 305.
- 228. Boldt, P. Chem. Ber. 1966, 99, 2322.
- 229. Reference 209, pp 124-125.
- 230. Vyvyan, J.R.; Loitz, C.; Looper, R.E.; Mattingly, C.S.; Peterson, E.A.; Staben, S.T.J. Org. Chem. 2004, 69, 2461.
- 231. Couladouros, E.A.; Strongilos, A.T.; Papageorgiou, V.P.; Plyta, Z.F. Chem. Eur. J., 2002, 8, 1795.

^{225.} References 209 and 210.



Oxidation of phenol leads to several interesting functional group transforms, including



3.3.B. Phenols

As discussed in section 2.11.E, phenols are conveniently prepared by hydrolysis of diazonium salts. There are also several oxidative methods that convert aromatic derivatives to phenols.²³² Direct hydroxylation can be accomplished by using free radical reagents such as a mixture of ferrous ion (Fe²⁺) and H₂O₂ (**Fenton's reagent**).²³³ The yields are usually poor, in the 5-20% range, and formation of biphenyls (a coupling product) predominates. Oxidation of benzene, for example, gave a low yield of phenol but a relatively large yield of biphenyl. In general, Fenton's reagent is not very useful for the preparation of phenols. Udenfriend et al introduced a modification of this procedure as a model for the biogenic hydroxylation of tyramine, using an oxygen-ferrous ion-ascorbic acid system in the presence of ethylenediaminetetraacetic acid (EDTA) (**Udenfriend's reagent**).^{234,233a} This reagent gave good yields of ortho- and paraphenolic derivatives from phenyl acetamide. An electrolytic version of this oxidation used anodic oxidation in the presence of Undenfriend's reagent and oxygen to convert tyramine to a mixture of hydroxytyramines and dihydroxytyramine (DOPA).²³⁵

Alkyl benzenes react with hydrogen peroxide, Lewis acid catalysts (such as boron trifluoride),²³⁶ or strong protonic acids such as trifluoroperoxyacetic acid^{237,233a} to give the corresponding phenol. Chambers et al. used trifluoroperoxyacetic acid to oxidize mesitylene (1,3,5-trimethylbenzene)

^{232.} Reference 20, pp 977-978.

^{233. (}a) Haines, A.H. Methods For the Oxidation of Organic Compounds, Academic Press, London, 1985, p 173; (b) Smith, J.R.L.; Norman, R.O.C. J. Chem. Soc. 1963, 2897.

^{234.} Udenfriend, S.; Clark, C.T.; Axelrod, J.; Brodie, B.B. J. Biol. Chem. 1954, 208, 731.

⁽a) Blanchard, M.; Bouchoule, C.; Djaneye-Boundjou, G.; Canesson, P. *Tetrahedron Lett.* 1988, 29, 2177;
(b) Maissant, J.M.; Bouchoule, C.; Canesson, P.; Blanchard, M. J. Mol. Catal., 1983, 18, 189;
(c) Maissant, J.M.; Bouchoule, C.; Blanchard, M. *Ibid.* 1982, 14, 333.

^{236.} Hart, H.; Buehler, C.A. J. Org. Chem. 1964, 29, 2397.

^{237.} Chambers, R.D.; Goggin, P.; Musgrave, W.K.R. J. Chem. Soc. 1959, 1804.

to 2,4,6-trimethylphenol in high yield based on consumed mesitylene (only a 17% conversion based on the peroxyacid).²³⁷ Similarly, McClure and Williams²³⁸ reported the oxidation of anisole to phenolic products in low yield (ortho- derivative in 27% yield and para- derivative in 7% yield), with a conversion of only 44%. Hart and co-workers found that the yield of 2,4,6-trimethylphenol from 1,3,5-trimethylbenzene was greatly improved (88% yield with good overall conversion) by using a mixture of boron trifluoride (BF₃) and trifluoroperoxyacetic acid (in dichloromethane at -7° C).²³⁶ This modification is probably the best method for peroxyacid oxidation of aromatic hydrocarbons to the corresponding phenol. Aluminum chloride is also an effective catalyst in this transformation, giving primarily a mixture of ortho- and parahydroxy derivatives.²³⁹

Phenol can be hydroxylated with potassium persulfate $(K_2S_2O_8)$ in alkaline media (the **Elbs persulfate oxidation**).²⁴⁰ In 1893 Elbs used ammonium persulfate to oxidize 2-nitrophenol to nitroquinol.²⁴¹ Later workers used the potassium salt,²⁴² which is now the reagent of choice, in order to obtain synthetically useful yields of para- hydroxy phenols. The initial oxidation product is the persulfate (154), which is hydrolyzed to hydroquinone (155) as shown.²⁴³ The ortho-product (a pyrocatechol derivative) is formed if the para-position is blocked, but the reaction is slower and the yields are in the 30-50% range.²⁴⁴ The presence of electron-withdrawing groups on the aromatic ring improves the yield, but electron-releasing groups such as methoxy (OMe) can also be tolerated.²⁴⁵



An alternative to direct hydroxylation is the thermal or photochemical decomposition of diacyl peroxides. Aryl derivatives react to give acyloxylation.²⁴⁶ *p*-Xylene was converted to **156** in the presence of cupric chloride,²⁴⁷ although the yield was only 24%. The benzoate ester in **156**

243. (a) Reference 233a, pp 180-181; (b) Baker, W.; Brown, N.C. J. Chem. Soc. 1948, 2303.

- 246. (a) Reference 233a, pp 177-178; (b) Rawlinson, D.J.; Sosnovsky, G. Synthesis 1972, 1.
- 247. Reid, C.G.; Kovacic, P. J. Org. Chem. 1969, 34, 3308.

^{238.} McClure, J.D.; Williams, P.H. J. Org. Chem. 1962, 27, 627.

^{239.} Kurz, M.E.; Johnson, G.J. J. Org. Chem. 1971, 36, 3184.

 ⁽a) Reference 233a, p 174; (b) Sethna, S.M. Chem. Rev. 1951, 49, 91; (c) Behrman, E.J. Beilstein J. Org. Chem. 2006, 2:22 (an on-line journal); (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-27.

^{241.} Elbs, K. J. Prakt. Chem. 1893, 48, 179.

^{242.} Chemische Fabrik auf Aktien vorm E. Schering: German Patents 81,068, 81,297 and 81,298: see Friedlander, Fortschritte der Teerfarbenfabrikation 1894-1897, 4th Part, pp 126, 127, 121 respectively, taken from citation 12 in reference 240b.

^{244.} Reference 233a, p 180.

^{245.} Baker, W.; Savage, R.I. J. Chem. Soc. 1938, 1602.

was easily hydrolyzed to the phenolic derivative. Lead tetraacetate [Pb(OAc)₄, abbreviated LTA, see sec. 3.7.C.i] gives a similar reaction, but this reagent gives the *O*-acetyl derivative from aryl derivatives. Polycyclic aromatics and aryl derivatives²⁴⁸,²⁴⁹ containing electron-releasing groups give the best yields of oxidation products.



The functional group transform for this reaction is

3.4. CONVERSION OF ALKENES TO EPOXIDES

The previous sections focused attention on the oxidation of a C–OH moiety to a C=O (carbonyl) group. Other functional groups are subject to oxidation, including the π bond of alkenes. There are several different oxidative functional group transformations that involve alkenes, including incorporation of one oxygen (epoxidation), two oxygens (dihydroxylation), or 1 oxygen and 1 nitrogen (aminohydroxylation), and finally, oxidative cleavage (usually to carbonyl derivatives). Sections 3.4.A-D will discuss various methods for the conversion of alkenes to epoxides (oxiranes)²⁵⁰ and the other functional group transformations will be discussed in succeeding sections.

3.4.A. Epoxides from Halohydrins

A simple method for producing epoxides uses the reaction of alkenes and hypohalous acids (generated by the reactions $Cl_2 + H_2O \rightarrow HOCl$ or $Br_2 + H_2O \rightarrow HOBr$) to give the trans-(or anti-) halohydrin as the major product. An example is the conversion of cyclohexene to 2-bromocyclohexanol (sec. 2.10.C). Subsequent treatment with a base such as sodium hydride generates the alkoxide, and displacement of the adjacent bromine via an S_N2 process (an *intramolecular* Williamson ether synthesis, sec. 2.6.A.i) gives cyclohexene oxide. The S_N2 nature of this base-induced cyclization restricts the reaction to halohydrins with a primary or secondary halide, and the halogen must be trans- to the hydroxyl group for epoxide formation. The halohydrin is often generated with aqueous NBS or NCS (see sec. 2.10.C). In a scalable synthesis of the potent fungicide 1-cytosinyl-*N*-malayamycin A by Loiseleur, Hanessian and

^{248.} Fieser, L.F.; Clapp, R.C.; Daudt, W.H. J. Am. Chem. Soc. 1947, 64, 2052.

^{249.} Ritcher, H.J.; Dressler, R.L. J. Org. Chem. 1962, 27, 4066.

^{250.} Reference 20, pp 915-927.

co-workers,²⁵¹ treatment of **157** with aqueous NBS gave bromohydrin **158** (one regioisomer is shown). Subsequent reaction of this mixture with NaOH led to formation of the epoxide unit in **159**. A protected form of the halohydrin can be used in this reaction, with the requisite alkoxide unit unmasked under controlled conditions. In Marino and co-worker's synthesis of (–)-macrolactin A,²⁵² deprotection of the *O*-silyl group (Sec 7.3.A.i) in **160** with cesium fluoride generated the alkoxide intermediate (**161**) *in situ*, and intramolecular displacement of the chloride on the terminal carbon atom gave epoxide **162** in 86% yield. It should be noted that this epoxide-forming reaction is not restricted to halide leaving groups, and sulfonate esters such as mesylate, tosylate, or triflate can be used. 1,2-Diols can be converted to a monosulfonate ester, and subsequent reaction with potassium hydroxide leads to an alkoxide that displaces the leaving group to give the epoxide.²⁵³



The functional group transform is simply:



3.4.B. Peroxide Induced Epoxidations

The reaction of peroxides with alkenes is a common method for the preparation of epoxides (oxiranes), but the nature of the peroxide is very important to the success of the oxidation. Peroxides are a source of electrophilic oxygen when they react with the nucleophilic π bond of an alkene. Hydrogen peroxide (H₂O₂) is a powerful oxidizing agent, with a reduction potential of 1.77 V¹⁷ for the following reaction:

252. Marino, J.P.; McClure, M.S.; Holub, D.P.; Comasseto, J.V.; Tucci, F.C. J. Am. Chem. Soc. 2002, 124, 1664.

Loiseleur, O.; Schneider, H.; Huang, G.; Machaalani, R.; Selles, P.; Crowley, P.; Hanessian, S. Org. Process Res. Dev. 2006, 10, 518,

^{253.} For an example of epoxide formation from a bromohydrin, taken from a synthesis of (-)-coriolin, see Mizuno, H.; Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I. J. Org. Chem. 1999, 64, 2648.

$$H_2O_2 + 2e^- + 2H^+ \rightarrow 2H_2O$$
 1.77 V

While most peroxide reactions involve homolytic cleavage of the O–O bond, generating free radicals (sec. 13.3), the reaction of H_2O_2 and its monosubstituted derivatives with an alkene can proceed via either a concerted or ionic mechanism.²⁵⁴ Three categories of peroxides are used

onic mechanism.²⁵⁴ Three categories of peroxides are used for epoxidation, hydrogen peroxide, alkyl hydroperoxides (**163**) and peroxyacids (**164**). The alkene can be viewed as a Lewis base in an initial reaction with the peroxide ROOH forming a coordination complex **165** that generates an

oxygen with a positive dipole. A heterolytic cleavage transfers that oxygen to the alkene, and subsequent proton transfer liberates the byproduct (water from hydrogen peroxide, an alcohol from an alkyl hydroperoxide, or a carboxylic acid from a peroxy acid). This sequence involves backside attack at oxygen in an S_N 2-like process (sec. 2.6.A.i).²⁵⁵ The relative rate of oxidation for various peroxide reagents is largely determined by the nature of the OR group in **165**,

$$RO-OH + H \longrightarrow \left[\begin{array}{c} H \\ H \\ R \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ R \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ R \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ R \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right]$$
 \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \left[\begin{array}{c} H \\ O \\ P \end{array} \right] \left[\begin{array}{c} H \\ O \end{array} \right] \longrightarrow \left[\begin{array}{c} H \\ O \end{array} \right] \\ \\[\begin{array}{c} H \\ O \end{array} \right] \end{array} \right] \left[\begin{array}{c} H \\ O \end{array} \right] \\ \\[\begin{array}{c} H \\ O \end{array} \right] \left[\begin{array}{c} H \\ O \end{array} \right] \left[\begin{array}{c} H \\ O \end{array} \right] \left[\begin{array}{c}

which behaves as a leaving group. The oxidizing power of the peroxide is inversely related to the pK_a of the conjugate acid generated by loss of the leaving group (ROH).²⁵⁶ It is difficult to compare different types of reagents, but a useful ranking of peroxides by their ability to convert alkenes to epoxides is^{256,255}

$$t-BuO - OH < HO - OH < Me - C - OOH < Ph - C - OOH < Cl O = CO3H < HO_3C - OOH < HO_2CO_2H < HO_2CHC : CHCO_3H < F_3C - C - OOH < HO_3C - OOH < HO_2CHC : CHCO_3H < F_3C - C - OOH < HO_3C - OOH < HO_2CHC : CHCO_3H < F_3C - C - OOH < HO_3C - OOH < HO_3C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3C - OOH < HO_3C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3C - OOH < HO_3C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : CHCO_3H < F_3C - C - OOH < HO_3CHC : C - OOH$$

Therefore, the strength of the peroxide reagent correlates more or less with its reactivity with alkenes. In the following sections, the emphasis will be on the synthetic utility and generality of peroxide induced reactions.

3.4.B.i. Hydrogen Peroxide. The reduction potential of oxygen¹⁷ is given by the following reactions:

$$O_2 + 2 H^+ + 2 e^- \rightarrow H_2O_2$$
 0.682 V

$$O_2 + 4 H^+ + 4 e^- \rightarrow 2 H_2O$$
 1.229 V

^{254.} Lewis, S.N. in Oxidation, Vol. 1, Augustine, R.L. (Ed.), Marcel Dekker, New York, 1969, p 214.

^{255.} Reference 254, p 215.

^{256.} Roberts, J.D.; Caserio, M.C. Basic Principles of Organic Chemistry, W.A. Benjamin, New York, 1965, p 301.

Hydrogen peroxide is used in water or water miscible solvents, but epoxidation of alkenes is slow unless metal ion catalysts such as vanadium pentoxide,²⁵⁷ tungsten trioxide,²⁵⁸ or molybdenum trioxide²⁵⁹ are used. In allylic alcohols, oxidation of the hydroxyl moiety is usually faster than oxidation of the alkene as in the oxidation of crotyl alcohol with hydrogen peroxide to give crotonaldehyde. The H_2O_2 oxidation of alkenes is not used unless the alkene is soluble in aqueous media since other peroxide reagents are more effective. Many of the comments presented in section 3.4.B.ii also apply to hydrogen peroxide.

There is an exception to the poor reactivity exhibited by hydrogen peroxide. When **166** was treated with 30% hydrogen peroxide in the presence of benzonitrile and potassium hydrogen carbonate, epoxide **167** was formed in 86% yield,²⁶⁰ in what is known as the **Payne epoxidation**.²⁶¹ The reagents used generate peroxybenzimidic acid *in situ*. This transformation was taken from Smith and co-worker's synthesis of (+)-calyculin A.²⁶⁰ *The Payne epoxidation is known to give a diastereofacial preference that is opposite to epoxidations with peroxyacids*. In this particular example, the epoxide **167** was a 3:1 (α : β) mixture of isomers at the epoxy carbon.



3.4.B.ii. Alkyl Hydroperoxides. Alkyl hydroperoxides are prepared by reaction of tertiary alcohols or alkenes with hydrogen peroxide, in the presence of sulfuric acid.²⁶² Alkyl hydroperoxides²⁶³ are also prepared by the autoxidation of alkanes with oxygen, which is also a potent oxidizing agent. The relatively stable reagent *tert*-butyl hydroperoxide (*t*-BuOOH, TBHP), for example was prepared in 75% yield (8% conversion) by reaction of isobutane with oxygen.²⁶⁴ In this case, the reaction was carried out in the liquid phase with di-*tert*-

^{257.} Kaman, A.J. British Patent 837 464, 1957, [Chem. Abstr. 55: 566f, 1961].

^{258. (}a) Payne, G.B.; Williams, P.H. J. Org. Chem. 1959, 24, 54; (b) Sergeev, P.G.; Bukreeva, L.M. Zh. Obshch. Khim., 1958, 28, 101 (Chem. Abstr. 52: 12758, 1958); (c) Raciszewski, Z. J. Am. Chem. Soc. 1960, 82, 1267; (d) Stevens, H.C.; Kaman, A.J. Ibid. 1965, 87, 734.

Carlson, G.J.; Skinner, J.R.; Smith, C.W.; Wilcoxen, Jr., C.H. U.S. Patent 2 833 787, 1958 [Chem. Abstr. 52: 16367d, 1958].

^{260.} Smith III, A.B.; Friestad, G.K.; Barbosa, J.; Bertounesque, E.; Duan, J.J.-W.; Hull, K.G.; Iwashima, M.; Qiu, Y.; Spoors, G.; Salvatore, B.A. *J. Am. Chem. Soc.* **1999**, *121*, 10478.

^{261.} Payne, G.B. Tetrahedron 1962, 18, 763.

 ⁽a) Milas, N.A.; Surgenor, D.M. J. Am. Chem. Soc. 1946, 68, 205; (b) Ross, H.; Huttel, R. Chem. Ber. 1956, 89, 2641.

^{263.} Reference 1, pp 17-32, 315-339 and 340-349.

^{264. (}a) Mayo, F.R. Acc. Chem. Res. **1968**, 1, 193; (b) Winkler, D.E.; Hearne, G.W. Ind. Eng. Chem. **1961**, 53, 655; (c) Bell, E.R.; Dickey, F.H.; Raley, J.H.; Rust, F.F.; Vaughan, W.E. Ibid. **1949**, 41, 2597.

butyl peroxide as an initiator (see sec. 13.3). Most tertiary alkanes react²⁶⁵ and probably involves a radical intermediate that reacts with oxygen²⁶⁵ and then with the alkane to give the hydroperoxide and regenerate the radical carrier (sec. 13.3).

 Table 3.4. Alkene Epoxidation by Transition Metal Catalyzed Reaction with Alkyl Hydroperoxides²⁶⁸

	RO-1	OH +	$\begin{bmatrix} R \\ R \end{bmatrix} \xrightarrow{M} C$					
R	Alkene	Solvent	М	<u>% M</u>	Conditions	% Epoxide		
Н	cyclohexene	dioxane	MoO ₃	10	50°C, 10h	38		
t-Bu	cyclohexene	dioxane	MoO ₃	12	80°C, 8h	99		
t-Bu	cyclohexene	neat	$MoO_2(acac)_2$	2	70°C, 1h	86		
cumyl	cyclohexene	PhEt	V-naphth.	0.03	90°C, 1h	97		
sec-Bu	cyclopentene	neat	V-octanoate	1	46°C, 6h	98		
t-Bu	1-octene	EtOAc	Na2MoO4/Na4(PMo12O40)	8	135°C, 2h	89		
cumyl	1-octene	cumene	MoO ₃	19	100°C, 6h	84		
tert-amyl	1-propene	neat	Mo-naphth.	2	130°C, 2h	78		
cumyl	2-methyl-2-pentene	neat	$Na_2MoO_4/Na_4(PMo_{12}O_{40})$	1.5	110°C, 0.75h	ı 97		
[Reprinted with permission of Hiatt, R., In Oxidation, Vol. 2, by Augustine, R.L.; Trecher, D.J. (eds.), Marcel Dekker, Inc., New York, 1971 , p. 124 by courtesy of Marcel Dekker Inc.]								

Tertiary alkylhydroperoxides are the most common reagents used to oxidize alkenes, since primary or secondary alkylhydroperoxides are susceptible to rearrangement and decomposition. Alkylhydroperoxides are relatively soluble in organic solvents, are more stable and are easier to handle than hydrogen peroxide.²⁶⁶ Both TBHP and cumyl hydroperoxide are commercially available and widely used. As with H₂O₂, the reaction of alkenes with hydroperoxides usually requires transition metal catalysts in order to form an epoxide.²⁶⁷ Several common catalyst systems are given in Table 3.4.²⁶⁸ Epoxidation with hydroperoxide gives racemic products in most cases. An important exception is the **Sharpless asymmetric epoxidation**, which generates chiral epoxides and will be discussed in sec. 3.4.D.i.

More highly substituted alkenes are epoxidized faster than less substituted alkenes.²⁶⁹ Reaction of **168** with TBHP and molybdenum hexacarbonyl selectively gave oxidation of the trisubstituted alkene, leading to **169**.²⁷⁰ Electron deficient alkenes are less reactive, as illustrated by the

 ^{265. (}a) Pritzkow, W.; Gröbe, K.H. Chem. Ber. 1960, 93, 2156; (b) Ester, W.; Sommer, A. U.S. Patent 3,259,661, British Patent 874,603 1961 [Chem. Abstr. 57: 1190e, 1962].

^{266.} Reference 254, p 216.

^{267.} Hiatt, R. in *Oxidation*, Vol. 2; Augustine, R.L.; Trecher, D.J. (Eds.), Marcel Dekker, New York, **1971**, pp 117-123.

^{268.} Reference 267, p 124.

^{269.} Reference 267, p 126.

^{270. (}a) Tolstikov, G.A.; Yur'ev, V.P.; Dzhemilev, U.M. Russ. Chem. Rev. 1975, 44, 319; (b) Sheng, M.N.; Zajacek, J.G. J. Org. Chem. 1970, 35, 1839.

epoxidation of geranial (102), which was epoxidized selectively at the unconjugated alkene moiety to give 170.²⁷¹ A neighboring group effect is possible when a coordinating group is present, as in allylic alcohols. Epoxidation of allylic alcohol 171, in Tadano and co-worker's synthesis of (+)-cheimonophyllon E,²⁷² gave a 78% yield of a 5.6:1 mixture of epoxides 172:173.



Such reactions involve initial coordination of the metal to both the allylic alcohol and the hydroperoxide, followed by displacement at the peroxy group by the alkene moiety.²⁷³ Although free radicals are not formally involved in the epoxidation, small amounts of radical decomposition products are sometimes observed.²⁷⁴ Sharpless proposed a mechanism for the vanadium-catalyzed epoxidation^{275a} that explains the stereoselectivity and provides insight into metal-catalyzed epoxidations. A vanadium(V) species such as 174 reacts with the allylic alcohol and TBHP to give 175 via displacement of two alkoxy ligands. Coordination of the second oxygen of the peroxide generates a metal peroxide, 176. The rate-determining step of this process is the epoxidation (176 \rightarrow 177), and the stereochemistry of the epoxide is determined at this point in the mechanism. Displacement of the epoxide probably proceeds via 178, to regenerate the vanadium catalyst.

^{271. (}a) Sheldon, R.A. J. Mol. Catal., 1980, 7, 107; (b) Reference 1, p 278.

^{272.} Takao, K.; Tsujita, T.; Hara, M.; Tadano, K. J. Org. Chem. 2002, 67, 6690.

 ⁽a) Gould, E.S.; Rado, M. J. Catal. 1969, 13, 238; (b) Masuo, F.; Kato, S. Yuki Gosei Kagaku Kyokai Shi 1968, 26, 367 [Chem. Abstr. 69: 18476u, 1968].

^{274.} Sheng, N.M.; Zajacek, J.C. *Advances in Chemistry Series No.* 76, American Chemical Society, Washington D.C., **1968**, and see citation 30 in reference 267, p 135.

 ⁽a) Sharpless, K.B.; Verhoeven, T.R. Aldrichimica Acta 1979, 12, 63; (b) Sharpless, K.B.; Michaelson, R.C. J. Am. Chem. Soc. 1973, 95, 6136.





In **176**, the alkene π bond will attack the peroxide moiety from the rear along the axis of the O–O bond.^{275a} In order to achieve backside attack, the allylic portion of the complex must deform as in **179**, giving an **O–C–C=**C bond angle of ~ 50°. This model predicts the diastereoselectivity for the epoxidation

of acyclic allylic alcohols such as **180**, which gave a mixture of **181** and **182** in a ratio of 71:29.^{275a} Examination of the transition states for the epoxidation of **180** (**183** and **184**) show a destabilizing interaction between methyl and hydrogen as compared to a hydrogen-hydrogen interaction. In **184**, a severe steric interaction exists between the alkenyl methyl and the methyl on the adjacent carbon, as well as the oxygen-vanadium complex. In **183**, the lower energy destabilizing interaction of the hydrogen and oxygen-vanadium complex suggests is lower in energy. If **183** is lower in energy, **181** is predicted to be the major product. The energy difference between **183** and **184** is not great, and significant amounts of **182** are observed.



The stereochemical consequences of this neighboring group effect were apparent in the transformation $171 \rightarrow 172$ above. The stereoselectivity is a bit easier to see when a cyclic alkene is involved. In a synthesis of phytuberin by Suárez and co-workers, allylic alcohol **185** was

treated with VO(acac)₂ and *t*-BuOOH in benzene, and an 85% yield of **186** was obtained.²⁷⁶ The hydroxyl unit directed the epoxidation to the top face of the bicyclic system, as shown. Note the oxidation of the sulfide to the corresponding sulfoxide (see Sec 3.9.A.i) during the epoxidation.



In basic media, peroxides react as acids and deprotonation gives a peroxide-anion that reacts with conjugated carbonyl derivatives via 1,4-addition (conjugate addition). Hydrogen peroxide reacts with base to give the hydroperoxide anion (HOO⁻), which adds to α , β -unsaturated ketones and aldehydes^{277,278} or esters.²⁷⁹ In a synthesis of (–)-phyllostine by Okamura and co-workers,²⁸⁰ the reaction of conjugated ketone **187** with basic hydrogen peroxide converted it to the corresponding epoxide (**189**) via an intermediate such as **188**, in which the enolate anion displaced the hydroxyl group to yield the epoxide. Note that the conjugate addition proceeded from the less hindered bottom face of the molecule.



For α , β -unsaturated aldehydes and ketones, the presence of a single carbonyl group is sufficient to activate the double bond to conjugate addition with hydroperoxide anions. This reactivity does not extend to α , β -unsaturated esters, however, and epoxidation does not occur unless two ester groups are present [such as is found with alkylidene malonate derivatives, CH₂=C(CO₂R)₂].²⁸¹ Peroxide anion epoxidation is usually stereoselective but rarely stereospecific.²⁸²

Alkyl hydroperoxides react with a suitable base to give a hydroperoxide anion (ROO⁻), directly analogous to the reactions of hydrogen peroxide. The reaction with conjugated carbonyl

- 278. Ohfune, Y.; Grieco, P.A.; Wang, C.-L.; Majetich, G. J. Am. Chem. Soc. 1978, 100, 5946.
- 279. Payne, G.B.; Williams, P.H. J. Org. Chem. 1959, 24, 284.
- 280. Okamura, H.; Shimizu, H.; Yamashita, N.; Iwagawa, T.; Nakatani, M. Tetrahedron 2003, 59, 10159.
- 281. Payne, G.B. J. Org. Chem. 1959, 24, 2048.
- 282. House, H.O.; Ro, R.S. J. Am. Chem. Soc. 1958, 80, 2428.

^{276.} Prangé, T.; Rodriguez, M.S.; Suárez, E. J. Org. Chem. 2003, 68, 4422. For a different example where the steric bias of the ring system does not cloud the issue of neighboring group assistance, see Kita, Y.; Furukawa, A.; Futamura, J.; Higuchi, K.; Ueda, K.; Fujioka, H. Tetrahedron Lett. 2000, 41, 2133.

^{277.} Nishigawa, M.; Grieco, P.A.; Burke, S.D.; Metz, W. J. Chem. Soc. Chem. Commun. 1978, 76.

derivatives is virtually the same for both HOO⁻ and ROO⁻, except for reactions with α , β unsaturated nitriles.²⁸³ Alkaline hydrogen peroxide converts such nitriles to epoxy amides,²⁸⁴ as in the reaction of acrylonitrile to give **191**, via initial formation of **190**.²⁸⁴ The related reaction of **192** with *tert*-butylhydroperoxide in basic solution, however, gave good yields of the epoxy-nitrile (**193**) rather than the amide.²⁸⁴



3.4.B.iii. Juliá-Colonna Epoxidation. A useful innovation involving the hydroperoxide anion epoxidation of conjugated carbonyl compounds uses a polyamino acid such as poly-*L*-alanine or poly-*L*-leucine in what is known as the Juliá-Colonna epoxidation.²⁸⁵ Originally, the reaction was done in a water-immiscible solvent such as toluene, in which the substrate was treated with an aqueous NaOH–H₂O₂ solution containing the polyamino acid. In general, harsh reaction conditions were required, including long reaction times and recovering the product from the gel-like catalyst as well as the catalyst was often difficult.²⁸⁶ These problems were diminished by using a biphasic system, that used a urea-hydrogen peroxide complex as the peroxide donor in an organic solvent containing DBU, along with the polyamino acid.²⁸⁷ This modification diminished the reaction time, alleviated the problems caused by the use of an aqueous base, and the product was easily recovered.²⁸⁶ Catalyst recovery remained a problem however.²⁸⁶ Gellar and Roberts modified the reaction by using silica gel as a solid carrier for the poly-*L*-leucine, and performed the reaction in THF.²⁸⁶ An example is the epoxidation of 194 to 195 in 93% yield, an improvement in both yield and reaction time when compared to the same reaction without the use of silica gel.²⁸⁶



The functional group transforms for this section are

(a) Bentley, P.A.; Bergeron S.; Cappi, M.W.; Hibbs, D.E.; Hursthouse, M.B.; Nugent, T.C.; Pulido, R.; Roberts, S.M.; Wu, L.E. Chem. Commun. 1997, 739; (b) Adger, B.M.; Barkley, J.V.; Bergeron S.; Cappi, M.W.; Flowerdew, B.E.; Jackson, M.P.; McCague, R.; Nugent, T.C.; Roberts, S.M. J. Chem. Soc. Perkin Trans. 1 1997, 3501; (c) Savizky, R.M.; Suzuki, N.; Bové, J.L. Tetrahedron: Asymmetry 1998, 9, 3967.

^{283.} Reference 254, p 232.

^{284.} Payne, G.B. Tetrahedron 1962, 18, 763.

^{285. (}a) Banfi, S.; Colonna, S.; Molinari, H.; Juliá, S.; Guixer, J. Tetrahedron 1984, 40, 5207. For recent reviews of this reaction, see (b) Pu, L. Tetrahedron: Asymmetry 1998, 9, 1457; (c) Ebrahim, S.; Wills, M. Tetrahedron; Asymmetry 1997, 8, 3163.

^{286.} Geller, T.; Roberts, S.M. J. Chem. Soc. Perkin Trans. 1 1999, 1397.

$$\underset{R}{\overset{O}{\longleftarrow}}_{R} \underset{R}{\overset{O}{\longleftarrow}}_{R} \underset{R}{\overset{O}{\overset}}_{R} \underset{R}{\overset{O}{\overset}_{R} \underset{R}{\overset{O}{\overset}}_{R} \underset{R}{\overset{O}{\overset}}_{R} \underset{R}{\overset{O}{\overset}_{R} \underset{R}{\overset}_{R} \underset{R}{\overset{O}{\overset}}_{R} \underset{R}{\overset{O}{\overset}_{R} \underset{R}{\overset}_{R} \underset{R}{} \underset{R}{}$$

3.4.C. Organic Peroxyacids

Peroxyacids are the most common reagents for the epoxidation of alkenes, which has been called the **Prilezhaev** (**Prileschajew**) reaction.^{288,289} This reaction does not require transition metal catalysis, and gives good yields of the epoxide. Peroxyacids such as 164 are prepared by reaction of carboxylic acids with hydrogen peroxide. An equilibrium is established during the reaction that favors the peroxyacid, although several alternative methods are available.^{288a} Strong acids such as formic or trifluoroacetic acid usually generate useful equilibrium concentrations of the peroxyacids upon reaction with hydrogen peroxide (the equilibrium is shifted to the right, forming 164). Most other alkyl and aryl acids, however, require catalytic amounts of strong mineral acids or *p*-toluenesulfonic acid to give the corresponding peroxyacid.²⁹⁰ Several peroxyacids have been commercially available (peroxyformic, peroxybenzoic, trifluoroperoxyacetic and *m*-chloroperoxybenzoic [mcpba, 196]), although the purity of these reagents can be as low as 45-60% depending of the purity of the peroxide used in their manufacture. Peroxyacids are significantly less acidic than their carboxylic acid counterparts.²⁹¹ The major byproduct of the alkene epoxidation reaction is the carboxylic acid precursor to the peroxyacid (see below). If necessary, this acid can be neutralized during an epoxidation reaction by addition of sodium acetate (or another buffering agent).



Trifluoroperoxyacetic acid (CF_3CO_3H) gives the strong organic acid trifluoroacetic acid (CF_3CO_2H) as a byproduct. This strong acid can catalyze rearrangement or other reactions of the epoxide product. Such secondary reactions are suppressed by addition of a buffer,

 ⁽a) Prileschajew, N. Berichte 1909, 42, 4811; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-76.

^{289. (}a) Swern, D. Chem. Rev. 1949, 45, 1 (see p 16); (b) Swern, D. Org. React. 1953, 7, 378.

^{290.} Reference 254, pp 215-220.

^{291.} White, R.W.; Emmons, W.D. Tetrahedron 1962, 17, 31.

which is usually the acid salt $(\text{RCO}_2^-\text{M}^+)$ of the acid by-product (sodium acetate with peroxyacetic acid, sodium benzoate with peroxybenzoic acid, and sodium trifluoroacetate with trifluoroperoxyacetic acid). Both sodium and potassium acetate are used as generic buffers, however, and sodium or potassium hydrogen phosphates can also be used. An example of a buffered reaction is the conversion of **197** to **198** in 81% yield, in Wipf and Li's synthetic studies for a synthesis of the tuberstemonone ring system.²⁹²

In one example of alkene epoxidation taken from a synthesis of (R)-7-hydroxycarvone from (S)- α -pinene by McIntosh and co-workers,²⁹³ **199** was converted to epoxide **200** with mcpba in dichloromethane buffered with sodium bicarbonate. Although mcpba is one of the more popular epoxidation reagents, shortages of concentrated hydrogen peroxide limit the availability of high purity mcpba, although less pure reagent is usually available as mentioned above. Development of alternative reagents has therefore been an ongoing process. The peroxyacid magnesium monoperphthalate (abbreviated MMPP,²⁹⁴ see the parent peroxy acid **216** below) was prepared by Brougham et al. and is an efficient reagent for the conversion of alkenes to epoxides in aqueous media.²⁹⁵



MOLECULAR MODELING: Facial Selectivity in Epoxidation

Facial selectivity is often an important consideration in epoxidation reactions, for example, in the conversion of **199** to **200**. While in some cases, a 2D sketch clearly suggests that one face of a molecule bond is more accessible than the other, in many other situations the 2D drawing may not be sufficient. The, mcpba epoxidation of the macrocyclic lactone shown below is one such case. In principle, substituents may shield both "top" and "bottom" faces of the double bond (see also problem 9p). However, the 3D model suggests that the ring atoms shield one face of the C=C unit, but the extent of shielding by substituents is not clear.



^{292.} Wipf, P.; Li, W. J. Org. Chem. 1999, 64, 4576.

^{293.} Lakshmi, R.; Bateman, T.D.; McIntosh, M.C. J. Org. Chem. 2005, 70, 5313.

^{294.} For reactions of MMPP and urea hydrogen peroxide, see Heaney, H. Aldrichimica Acta 1993, 26, 35.

^{295.} For an example, see Brougham, P.; Cooper, M.S.; Cummerson, D.A.; Heaney, H.; Thompson, N. *Synthesis* 1987, 1015.

MOLECULAR MODELING: Facial Selectivity in Epoxidation, con't.

Examine the 3D model provided on screen. (This corresponds to the lowest-energy conformer resulting from examination of all conformers using molecular mechanics.) You might find it helpful to switch to a space-filling model to get a better idea of the difference between the two faces (select *Space Filling* from the **Model** menu at the top of the screen). Before you do so, orient the molecule as in the sketch, placing the trans-double bond to the top-left and the lactone carbonyl to the bottom. Is one face more shielded that the other? If so, which diastereomeric epoxide is likely to be observed?

A major advantage of using peroxyacids is the rapid epoxidation of unfunctionalized alkenes, which are normally unreactive with hydrogen peroxide or alkyl hydroperoxides without the presence of transition metal catalysts.²⁹⁶ The reaction probably proceeds via a concerted mechanism as proposed by Bartlett,²⁹⁷ in which the alkene and the oxygen of the OH unit in **164** coordinate and the epoxide is formed with loss of the carboxylic acid The transition state for this reaction has been analyzed using computational methods²⁹⁸ and it is usually represented by **201**. The geometry of the transition state dictates a syn delivery of oxygen, without changing the geometry of the alkene. Other mechanisms have been proposed as well.²⁹⁹



As first noted with hydroperoxides, neighboring group effects are also important in reactions of peroxyacids. Reexamination of the epoxidation of **180** using mcpba rather than TBHP reveals that the peroxyacid gave a 95:5 mixture of **181** and **182**. Using mcpba rather than TBHP led to a slight increase in diastereoselectivity for the reaction, although this depends on the substitution pattern of the alkene. Sharpless and co-workers proposed an intermediate based on

^{296.} Reference 254, p 223.

^{297.} Bartlett, P.D. Rec. Chem. Progr. 1950, 11, 47.

^{298.} Freccero, M.; Gandolfi, R.; Sarzi-Amadè; Rastelli, A. J. Org. Chem. 2000, 65, 8948.

⁽a) Kwart, H.; Hoffman, D.M. J. Org. Chem. 1966, 31, 419; (b) Hanzlik, R.P.; Shearer, G.O. J. Am. Chem. Soc. 1975, 97, 5231; (c) Dryuk, V.G. Tetrahedron 1976, 32, 2855; (d) Bach, R.D.; Canepa, C.; Winter, J.E.; Blanchette, P.E. J. Org. Chem. 1997, 62, 5191.

202 (a generic model for any peroxyacid, although peroxyacetic acid is used here),²⁷⁵ in which one plane (defined by the peroxyacid molecule in plane B) is oriented at an angle of $\approx 60^{\circ}$ to the plane of the π bond (plane A). One of the non-bonding electron pairs on oxygen (electron pair a) lies in plane B and is properly situated to begin bonding with the alkene carbon. The other lone pair electrons (electron pair b) is positioned so it can hydrogen bond with the allylic hydroxyl group, as in **203** or in **204**. The selectivity of epoxidations involving peroxy acids was previously explained by hydrogen bonding to O² or O³ in **202**.³⁰⁰ If backside displacement of the peroxy bond is required, hydrogen bonding to O² or O³ is not possible. A hydrogen bond to O¹, however, will have a dihedral angle for the **O**–**C**–**C**=**C** bond from ~ 50-130°, with 120° predicted as optimal (shown in **203** and **204**).^{275a} In **203**, the destabilizing methyl-hydrogen interaction is less than the methyl-alkenylmethyl interaction in **204**. The peroxy moiety will interact with the alkenylmethyl moiety in both cases. The greater destabilizing interaction in **204** leads to a predominance of **181** (from **203**) with only small amounts of **182** (from **204**).



Alkenes with more substituents are electron rich, and react with peroxyacids faster than less substituted alkenes. In general, the relative rate of epoxidation increases with the nucleophilic character of the alkene³⁰¹ (CH₂=CH₂ has a relative rate of 1, RCH=CH₂ = 24, RCH=CHR = 500, R₂C=CH₂ = 500, R₂C=CHR = 6500, and R₂C=CR₂ = >>6500).³⁰² Tri- and tetrasubstituted double bonds are rapidly epoxidized with peroxy acids, but peroxybenzoic acids are more effective than peroxyalkanoic acids. If a molecule contains two alkene moieties, the more highly substituted alkene is epoxidized faster. 1,2-Dimethyl-1,4-cyclohexadiene, for example, gave primarily the tetrasubstituted epoxide upon reaction with mcpba.³⁰³ This preference is seen in Sarpong and Simmons' synthesis of salviasperanol,³⁰⁴ where the tetrasubstituted diene in **205** was epoxidized in preference to the disubstituted C=C unit to give **206**. In this case, the trisubstituted alkene allylic to the OH is epoxidized in preference to the hydroxyl (Sec. 6.4).

303. Paquette, L.A.; Barrett, J.H. Org. Syn. Coll. Vol. 5, 1973, 467.

^{300.} Chamberlain, P.; Roberts, M.L.; Whitham, G.H. J. Chem. Soc. B 1970, 1374.

^{301.} Swern, D. J. Am. Chem. Soc. 1947, 69, 1692.

^{302.} Reference 254, p 225.

^{304.} Simmons, E.M.; Sarpong, R. Org. Lett. 2006, 8, 2883.



MOLECULAR MODELING: Selectivity in Epoxidation Reactions

Both positional and stereoselectivity in epoxidation reactions can be anticipated using local ionization potential maps. This colors an electron density surface which gives the overall molecular size and shape (where a reagent can approach) with the value of the local ionization potential (the energy required to expel an electron from a given location on the surface). By convention, the surface is colored "red" for small values of the local ionization potential (loosely-bound electrons) and "blue" for large values of the local ionization potential (tightly bound electron). Red regions are nucleophilic and are more likely to donate electrons to an electrophile such as the electrophilic oxygen of a peroxyacid.

Consider for example epoxidation of diene shown below.



While this reaction can give rise to one of four products depending on which face of which double bond is most susceptible, the authors characterize only a single product derived from epoxidation of the double bond on the five-membered ring *anti* to both alkyl substituents. (see homework problem 9f). They further note while that epoxidation at the five-member ring is clean, other (unspecified) products are observed.

Examine the local ionization potential map for this diene. It is depicted as a transparent model, allowing the underlying structures to be seen. You can switch to a solid model, allowing the maps to be seen more easily, by *clicking* on the map and then selecting *Solid* for the *Style* menu at the bottom of the screen. For which double bond, that belonging to the five or seven member ring, is the local ionization potential smaller? For which face on this ring, *syn* or *anti* to the two alkyl groups, is the local ionization potential smaller? *Click* on different regions on the map and the value of the local ionization potential will be displayed at the bottom of the screen. Does addition of the peroxyacid to the preferred face of the preferred double bond yield the observed epoxidation product? According to the local ionization potential map, are any other sites on the diene likely to be competitive? If so, identify the product(s) that would result.

Optional: Is the observed epoxidation product also the thermodynamic product? Obtain energies for all four products. Is this reaction likely to be thermodynamically controlled?

Monosubstituted alkenes are generally less reactive and epoxidation may require the use of a strong peroxyacid such as trifluoroperoxyacetic acid, although mcpba is often effective.³⁰⁵ For most alkenes mcpba is a good all-purpose peroxyacid. Even highly hindered alkenes can be epoxidized.³⁰⁶ If there is no possibility of hydrogen bonding, the peroxyacid usually approaches the alkene from the least hindered face, ^{307,308} and such reactions are highly diastereoselective. Selectivity depends on the peroxyacid used as well as the reaction conditions. Epoxidation of **207** with mcpba in THF, for example, gave an 84% yield of epoxide **208** with only 4% of **209** in an example taken from the Azuma et al. synthesis of sphingosine.³⁰⁹ When done in benzene, the reaction was complete in only 4 hours but the ratio of **208/209** was 82:18. Although **208** was the major product in all cases, diastereoselectivity varied with solvent and reaction time and in some cases the stereoselectivity was much lower.



The presence of electronegative substituents on the double bond lowers the nucleophilicity of the alkene and decreases the rate of epoxidation.^{310,311} Vinyl chlorides,³¹² vinyl acetates³¹³ and vinyl ethers³¹⁴ react slower than unsubstituted double bonds.³¹⁵ Glycidic esters (epoxy esters) such as **210**, for example, can be formed from conjugated esters such as ethyl 2-butenoate using mcpba³¹⁶ or trifluoroperoxyacetic acid, with a disodium phosphate or a sodium or potassium

 $Me \xrightarrow[CO_2Et]{RCO_3H} O \xrightarrow[Me]{O} CO_2Et$

hydrogen phosphate buffer.³¹⁷ The epoxides resulting from epoxidation of these substrates are often labile, however, and can rearrange to an α -halo or α -carboalkoxy ketone in unbuffered reactions.³¹⁸

- 306. Abruscato, G.J.; Tidwell, T.T. J. Org. Chem. 1972, 37, 4151.
- 307. (a) Christenson, P.A.; Willis, B.J. J. Org. Chem. 1979, 44, 2012; (b) Hickinbottom, W.J.; Wood, D.G.M. J. Chem. Soc. 1953, 1906.
- 308. Swindell, C.S.; Britcher, S.F. J. Org. Chem. 1986, 51, 793.
- 309. Azuma, H.; Tamagaki, S.; Ogino, K. J. Org. Chem. 2000, 65, 3538.
- 310. Ogata, Y.; Tabushi, I. J. Am. Chem. Soc. 1961, 83, 3440.
- 311. White, R.W.; Emmons, W.D. Tetrahedron 1962, 17, 31.
- 312. Mousseron M.; Jacquier, R. Bull. Chim. Soc. Fr. 1950, 698.
- 313. Shine, H.J.; Hunt, G.E. J. Am. Chem. Soc. 1958, 80, 2434.
- 314. Stevens, C.L.; Tazuma, J. J. Am. Chem. Soc. 1954, 76, 715.
- 315. Moffett, R.B.; Slomp, Jr., G. J. Am. Chem. Soc. 1954, 76, 3678.
- 316. Schwartz, N.N.; Blumbergs, J.H. J. Org. Chem. 1964, 29, 1976.
- 317. Emmons, W.D.; Pagano, A.S. J. Am. Chem. Soc. 1955, 77, 89.
- 318. (a) McDonald, R.N.; Schwab, P.A. J. Am. Chem. Soc. 1963, 85, 820, 4004; (b) Stevens, C.L.; Dykstra, C.J. Ibid. 1953, 75, 5975; (c) Gardner, P.D. Ibid. 1956, 78, 3421.

^{305.} Reference 254, p 226.

Conjugation diminishes the reactivity of an alkene in epoxidation reactions.³¹⁹ Conjugated esters, for example, are less reactive than simple alkenes due to the electron-withdrawing effect of the carbonyl. Isolated (unconjugated) alkenes are usually epoxidized before conjugated alkenes as seen in the reaction of **211** to give **212**, taken from the synthesis of (+)-salvadione-A by Majetich and co-workers.³²⁰



The neighboring group effect observed in the reaction of allylic alcohols and hydroperoxides is observed with peroxyacids, as it was in the epoxidation reactions discussed in previous sections. The so-called **Henbest rule** states that allylic alcohols exert a strong directing influence upon epoxidation when peroxyacids are used.³²¹ *However, this effect does not operate in medium sized rings, and rings with significant flexibility tend to give the trans-product.*³²² An example involving a cyclopentenol derivative is shown in a synthesis of (+)-streptazolin by Miller and Li.³²³ Epoxidation of **213** with mcpba and sodium bicarbonate led to a 92% yield of **214** with



epoxidation occurring on the same face as the ring hydroxyl group. Functional groups other than hydroxyl are capable of a neighboring group effect. The relative ability of a group adjacent to a double bond to coordinate with a peroxy acid in such a way that there is syn delivery of the epoxide oxygen is³²⁴

 $OH > CO_2H > CO_2R > OCOR$

Occasionally, the proximity of the alkene to another reactive group can lead to a competing reaction. In the case of **215**, the hydroxyl is too far away to show a significant neighboring group effect and epoxidation with perphthalic acid (**216**) proceeded from the exo-face.^{302,325} The trifluoroacetic acid byproduct of the epoxidation protonated the exo-epoxide (see **217**), however, allowing the hydroxyl unit on the other side of the molecule to react as shown to give alcohol-ether **218** as the final product.^{302,325} This type of secondary reaction can be prevented

^{319.} Hiyama, T.; Kanakura, A.; Yamamoto, H.; Nozaki, H. Tetrahedron Lett. 1978, 3051.

^{320.} Majetich, G.; Wang, Y.; Li, Y.; Vohs, J.K.; Robinson, G.H. Org. Lett. 2003, 5, 3847.

^{321.} Henbest, H.B.; Wilson, R.A. J. Chem. Soc. 1957, 1958.

^{322.} Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. J. Am. Chem. Soc. 1979, 101, 159.

^{323.} Li, F.; Miller, M.J. J. Org. Chem. 2006, 71, 5221.

^{324.} Reference 233a, p 101.

^{325.} Rosowsky, A. in *Heterocyclic Compounds, Part 1*, Weissberger, A. (Ed.), Wiley Interscience, New York, *1964*, pp 1-523. For another example, see Tinsley, S.W. J. Org. Chem. **1957**, *24*, 1197.

by protection of the OH unit (sec. 7.3.A) or, in some cases, buffering will minimize acidcatalyzed secondary processes.



The functional group transforms are



3.4.D. Asymmetric Epoxidation Reactions

The previous section described the metal catalyzed epoxidation of allylic alcohols by alkyl hydroperoxides, and **202** was proposed as a model to predict the diastereoselectivity of these reactions. In the cases presented, the epoxidation reaction was diastereoselective but not enantioselective (sec. 1.4.F), generating racemic epoxides. To achieve asymmetric induction one must control both the orientation of the alkene relative to the peroxide and also the face of the substrate from which the electrophilic oxygen is delivered. Such control can be accomplished by providing a chiral ligand that will coordinate to the metal catalyst, which is also the peroxide and the alkene unit. There are two major asymmetric epoxidation reactions currently used in synthesis. One can be applied only to allylic alcohols and is the prototype for asymmetric induction in these systems. The other is a procedure that can be applied to simple alkenes. Both use a metal-catalyzed epoxidation that employs alkyl hydroperoxides.

3.4.D.i. Sharpless Asymmetric Epoxidation.³²⁶ The epoxidation reactions described in previous sections generated racemic products even when they were highly diastereoselective. The reagents presented simply did not provide the facial bias required for asymmetric induction. That changed in 1980, when Sharpless reported that epoxidation of allylic alcohols with *tert*-butyl hydroperoxide, catalyzed by tetraisopropoxy titanium (IV) $[Ti(Oi-Pr)_4]$, gave the epoxy alcohol with high enantioselectivity when (+)- or (–)-diethyl tartrate was added to the reaction medium.^{327,328,275} Reaction of geraniol (101) under these conditions, in the presence of L-(+)-diethyl tartrate (DET), gave **219** in 77% yield and 95% ee for the (2*S*,3*S*) stereoisomer.³²⁷ Note

^{326.} The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-85.

^{327.} Katsuki, T.; Sharpless, K.B. J. Am. Chem. Soc. 1980, 102, 5974.

^{328. (}a) Rossiter, B.E.; Katsuki, T.; Sharpless, K.B. *J. Am. Chem. Soc.* **1981**, *103*, 464; (b) Martin, V.S.; Woodard, S.S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K.B. *Ibid.* **1981**, *103*, 6237.

that the natural isomer of diethyl tartrate [L-(+)-] is readily available as is the *unnatural* tartrate [(D-(-)-]], although the latter is significantly more expensive. When the epoxy alcohol product is water soluble, optical activity and yield were diminished.³²⁷



When the previously cited transition structure **202** is applied to the asymmetric epoxidation of allylic alcohols, it must be modified to include binding of the peroxide, the allylic alcohol and also the chiral tartrate. The metal in this reagent is titanium rather than vanadium, and tetraisopropoxy titanium was found to react with two equivalents of diethyl tartrate to form a species such as 220, where OR = Oi-Pr and $CO_2R = CO_2Et$.^{329,330} The tartrate can bind to titanium from either the bottom or the top face.³³⁰ The nature of the OR and E groups will determine the facial preference and, thereby, the selectivity of the epoxidation. When **220** reacted with TBHP and an allylic alcohol, two equivalents of 2-propanol were displaced to generate 221. The peroxide linkage and the allylic alcohol in 221 are bound to the metal and backside attack of the alkene moiety along the axis of the O-O bond will lead to the epoxide. The titanium serves as a template for the reaction and the presence of the chiral tartrate makes 221 a chiral molecule. If the ester groups shown as E in 221 were not present, the allylic alcohol could bind to titanium on both the top and the bottom. When the metal binds tartrate (the source of the E groups in **220** and **221**), a pocket is created that allows the allylic alcohol and the peroxide to coordinate. The face opposite this pocket is too sterically hindered for efficient binding, so binding occurs preferentially from one face and the usual backside attack leads to a single enantiomer. The extent of this enantioselectivity is determined by the extent to which binding of the allylic alcohol and peroxide is limited to a single face. Sharpless showed that this process proceeds by a series of reversible (equilibrium) steps for binding alcohol, alkoxy groups, and peroxide to titanium.³³⁰



[Reprinted with permission from Burns, C.J.; Martin, C.A.; Sharpless, K.B. J. Org. Chem. 1989, 54, 2826. Copyright © 1989 American Chemical Society.]

 ⁽a) Burns, C.J.; Martin, C.A.; Sharpless, K.B. J. Org. Chem. 1989, 54, 2826; (b) Carlier, P.R.; Sharpless, K.B. Ibid. 1989, 54, 4016.

^{330.} Johnson, R.A.; Sharpless, K.B. Comprehensive Organic Synthesis Volume 7, Chapter 3.2, Asymmetric Epoxidations, Pergamon Press, Oxford, **1990**.

Sharpless provided an empirical model that enables one to predict the stereochemistry of the epoxide formed in this reaction. When using the natural L-(+)- (2*R*, 3*R*) tartrate, the allylic alcohol should be oriented as shown for 222, with the hydroxyl group in the plane of the double bond and to the right.^{328c} With this orientation, the (+)-tartrate (in this case diisopropyl tartrate, DIPT) delivers oxygen (remember it is the alkene that attacks the peroxide) from the face bearing the hydroxyl (the *re-si* face) to give primarily the anti-product (223) with trace amounts of the syn-isomer 224.^{328c} If the model in 222 is drawn again as 225 and 226 for the reaction that forms 223 and 224, the source of this selectivity can be determined. In 225, the CO₂*i*-Pr \leftrightarrow H interaction is small compared to the cyclohexyl \leftrightarrow CO₂*i*-Pr interaction in 218 (see 217B and 218B; hydrogen atoms removed for clarity). The preference for 225 leads to approach of peroxide oxygen from the si face of the alkene. In 225, the (*S*)-chiral center of the allylic alcohol gives a better fit with the stereogenic center of the tartrate (the chirality is matched) than does the (*R*)-stereogenic center of the alcohol in 226. Such matching of stereogenic centers is referred to as **consonance** (as in 225) whereas the interaction of mismatched stereogenic centers (in 226) is called **dissonance**.



This model is formally illustrated in Figure 3.1^{330} for DET, which shows the propensity for (+)-DET to give the anti-product from the *re-si* face and for (–)-DET to give the syn-product from the *si-re* face. Figure 3.1 illustrates consonance when the chirality of natural (+)-DET leads to faster reaction from the *si* face to give the anti-product. Conversely, the chirality of (–)-DET is mismatched to the *si* face making that reaction slower, although it is matched to the *re* face and that epoxidation is faster. Allylic alcohol **222**, for example, reacts 104 times faster with (L)-(+)-DIPT than the enantiomer (**229**), due to the consonance with the (*S*)-enantiomer (and the corresponding dissonance of this tartrate with the (*R*)-enantiomer). This difference in reactivity led to **kinetic resolution** (one enantiomer reacts faster to give a predominance of that epoxide) of the allylic alcohols.^{328c} In general, the additive (L)-(+)-DIPT reacts best with allylic

alcohols of the type represented by generic structure **228**, where (*D*)-(–)-DIPT would be the choice for **227**. The (*R*)-enantiomer of alcohol **222** is **229**, and it reacts with (*L*)-(+)-DIPT to give a mixture of diastereomers (**230** and **231**), with the syn-isomer (**231**) predominating (38:62).



Figure 3.1. Facial selectivity on allylic alcohols for (+) and (-)-diethyl tartrate. [Reprinted with permission from Johnson, R.A.; Sharpless, K.B. *Comprehensive Organic Synthesis*, Volume 7, Chapter 3.2, *Asymmetric Epoxidations*, Pergamon Press, Oxford, **1990**. Copyright 1990, with permission from Elsevier Science.]



The rate for reaction of one enantiomeric allylic alcohol increases in comparison with the other, as the size of the alkyl group on tartrate increases (Me \rightarrow Et \rightarrow *i*-Pr).³³⁰ Inspection of **230/231** reveals that changing the tartrate ester from methyl to ethyl and then to isopropyl increases the steric preference for one enantiomer (see above). The CO₂R¹ \leftrightarrow cyclohexyl interaction is greater when R¹ is isopropyl than when R¹ is methyl, which will lead to faster binding of **222** than of **229** and faster epoxidation. Figure 3.1 also illustrates the source of kinetic resolution in the matched and mismatched interaction of (+)- or (-)-DET with a chiral allylic alcohol. This

methodology can be applied in a variety of synthetic manipulations.^{331,332}

Sharpless asymmetric epoxidation is a reaction where an achiral precursor is converted to a chiral substrate with high enantioselectivity. This discovery led to the application of the basic principles of ligand coordination to a metal and ligand transfer to a variety of other reactions. There are many synthetic examples of Sharpless asymmetric epoxidation. One is the conversion of **232** to **233**, in Knapp and co-worker's synthesis of the liposidomycin diazepanone nucleoside,³³³ mediated by (–)-diethyl D-tartrate (DET). A second example uses the enantiomer of diethyl tartrate [(+)-diethyl L-tartrate (DET)] and is taken from Crimmins and Caussanel's synthesis of FD-891, where allylic alcohol **234** was converted to **235** in 72% yield.³³⁴ A last example, taken from Hoye and Ye's synthesis of (+)-parviflorin,³³⁵ shows that a double-Sharpless epoxidation can be accomplished, as in the conversion of **236** to **237** in 87% yield in ~ 97% ee.



3.4.D.ii. Jacobsen-Katsuki Asymmetric Epoxidation. The Sharpless asymmetric epoxidation only works with allylic alcohols, as illustrated by the conversion of **232** to **233**. By changing the catalyst it is now possible to convert simple alkenes to the corresponding epoxide with high asymmetric induction. In independent work, Katsuki and Jacobsen showed that asymmetric epoxidation occurs using manganese-salen catalysts in the presence of *tert*-butylhydroperoxide,

- 334. Crimmins, M.T.; Caussanel, F. J. Am. Chem. Soc. 2006, 128, 3128.
- 335. Hoye, T.R.; Ye, Z. J. Am. Chem. Soc. 1996, 118, 1801.

^{331. (}a) Sharpless, K.B.; Behrens, C.H.; Katsuki, T.; Lee, A.W.M.; Martin, V.S.; Takatani, M.; Viti, S.M.; Walker, F.J.; Woodard, S.S. *Pure Appl. Chem.* 1983, 55, 589; (b) Reference 265; (c) Behrens, C.H.; Sharpless, K.B. *Aldrichimica Acta* 1983, 16, 67.

^{332.} Katsuki, T.; Lee, A.W.M.; Ma, P.; Martin, V.S.; Masamune, S.; Sharpless, K.B.; Tuddenham, D.; Walker, F.J. *J. Org. Chem.* **1982**, *47*, 1373.

^{333.} Knapp, S.; Morriello, G.J.; Doss, G.A. Org. Lett. 2002, 4, 603.

where salen = bis(salicylidene)ethylenediamine. A typical catalyst is **238** where R¹ can be an aryl group or cycloalkyl, bromine, trialkylsilyloxy and other groups. The manganese-salen catalyst **239** is called the **Jacobsen catalyst**, [*N*,*N*²-bis(3,5-di-*tert*-butylsalicylidene)-1,2-cyclohexane-diamine]manganese(III)] chloride. Metals other than manganese have also been used. It has been established that the order of mixing of the components is mechanistically important.³³⁶ Although Mn(IV)-salen complexes are formed in the absence of alkenes, they play a minor role in common epoxidation reactions.³³⁶

Simple alkenes are oxidized with high asymmetric induction (the so- called the **Jacobsen-Katsuki reaction**).³³⁷ In a typical transformation, styrene was converted to styrene oxide (**240**) in 89% yield and 86% ee using 2-8 mol% of **238** ($R^1 = Ph$, $R^2 = OSi(i-Pr)_3$, with the combination of mcpba and *N*-methylmorpholine *N*-oxide (NMO) as the oxidizing agent.^{337k} Jacobsen used this procedure in a synthesis of leucotrine A₄ (LTA₄).^{337d} In that synthesis, **241** was oxidized with sodium hypochlorite (NaOCl) and 20% 4-phenylpyridine *N*-oxide at pH 11.3, using 4% of the **239** catalyst). Epoxide **242** was obtained in 62% yield (82% ee and a trans/cis ratio of 8:1).^{337d} Katsuki found that the degree of enantioselection in some Mn-salen complexes depends on the conformation of the ligand and the nucleophilicity of the substrate,³³⁸ which is explained by enthalpy and entropy factors.



^{336.} Adam, W.; Mock-Knoblauch, C.; Saha-Möller, C.R.; Herderich, M. J. Am. Chem. Soc. 2000, 122, 9685.

⁽a) Hatayama, A.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. Synlett 1992, 407; (b) Yamada, T.; Imagawa, K.; Nagata, T.; Mukaiyama, T. Chem. Lett. 1992, 2231; (c) Schwenkreis, T.; Berkessel, A. Tetrahedron Lett. 1993, 34, 4785; (d) Chang, S.; Lee, N.H.; Jacobsen, E.N. J. Org. Chem. 1993, 58, 6939; (e) Sasaki, H.; Irie, R.; Katsuki, T. Synlett 1994, 356; (f) Chang, S.; Heid, R.M.; Jacobsen, E.N. Tetrahedron Lett. 1994, 35, 669; (g) Hosoya, N.; Hatayama, A.; Irie, R.; Sasaki, H.; Katsuki, T. Tetrahedron 1994, 50, 4311; (h) Brandes, B.D.; Jacobsen, E.N. J. Org. Chem. 1994, 59, 4378; (i) Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. Tetrahedron 1994, 50, 11827; (j) Brandes, B.D.; Jacobsen, E.N. Tetrahedron Lett. 1995, 36, 5457; (l) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006 p ONR-48; (m) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 344-345.

^{338.} Nishida, T.; Miyafuji, A.; Ito, Y.N.; Katsuki, T. Tetrahedron Lett. 2000, 41, 7053.



This epoxidation reaction is useful for disubstituted alkenes and also for trisubstituted alkenes.^{337h} Epoxidation of trisubstituted alkenes proceeds with absolute asymmetric induction that was opposite to that observed with cis- or trans-disubstituted alkenes.^{337h} Jacobsen suggested a general, skewed side-on approach transition state model³³⁹ for the epoxidation that proceeds by a stepwise radical mechanism.^{339b} Song et al. introduced a variation in which catalyst **239** is used in an ionic liquid consisting of 1,3-dialkylimidazolium cations with a PF₆⁻ counterion,³⁴⁰ which allows the manganese-salen catalyst to be easily recycled. The mechanism of this reaction has been discussed elsewhere.³⁴¹ As mentioned above, radical intermediates have been postulated.³⁴² There is no doubt that this reaction will increase in importance in syntheses. Note that manganese-salen catalysts have been used in epoxide ring-opening reactions.³⁴³

Salen catalysts are increasingly used for kinetic resolution. The reaction of a racemic epoxide with cobalt salen catalysts in aqueous media leads to selective hydrolysis of one enantiomer, giving a diol and one enantiopure epoxide. An example of this **Jacobsen hydrolytic kinetic resolution** is the conversion of **243** to 47% of enantiopure diol **245** and 49% of enantiopure epoxide **246**, using 0.01 equivalents of salen catalyst **244**³⁴⁴ in Smith and Kim's synthesis of (–)-indolizidine 223AB.



3.4.D.iii. Epoxidation with Dioxiranes. There is growing interest in non-metal based epoxidations.³⁴⁵ Dialkyl dioxiranes³⁴⁶ such as **248** and **251** are versatile oxidizing agents

- 340. Song, C.E.; Roh, E.J. Chem. Commun. 2000, 837.
- 341. See Linker, T. Angew. Chem,. Int. Ed. 1997, 36, 2060 for a discussion of the mechanism.
- 342. Cavallo, L.; Jacobsen, H. Angew. Chem. Int. Ed. 2000, 39, 589.
- 343. Jacobsen, E.N. Acc. Chem. Res. 2000, 33, 421.
- 344. Smith III, A.B.; Kim, D.-S. J. Org. Chem. 2006, 71, 2547.
- 345. For a recent review, see Dalko, P.; Moisan, L. Angew. Chem. Int. Ed.. 2001, 40, 3726.
- 346. (a)Adam,W.;Curci,R.;Edwards,J.O.*Acc. Chem. Res.* **1989**, 22,205;(b)Murray,R.W.*Chem. Rev.* **1989**, 89,1187; (c)Curci,R.;Dinoi,A.;Rubino,M.F.*Pure.Appl. Chem.* **1995**, 67,811;(d)Denmark,S.E.;Wu,Z.*Synlett* **1999**,847.

^{339. (}a) Groves, J.T.; Myers, R.S. J. Am. Chem. Soc. 1983, 105, 5791; (b) Jacobsen, E.N.; Deng, L.; Furukawa, Y.; Martínez, L.E. Tetrahedron 1994, 50, 4323

that can be generated from an oxidant and a ketone. The most commonly used oxidant in this epoxidation is potassium peroxomonosulfate (KHSO₅) generated from Oxone[®] (2KHSO₅•KHSO₄•K₂SO₄). When the dioxirane is generated in the presence of an alkene, an epoxide is formed. Dimethyldioxirane (**248**) is the parent of dialkyl dioxiranes used for the epoxidation of alkenes.³⁴⁷ In a synthesis of merrilactone A,³⁴⁸ Inoue and co-workers converted **247** to epoxide **249** in >95% yield (dr > 13:1) using **248**. If done in the presence of a chiral ketone, a chiral epoxide is formed.³⁴⁹ In 1984, Curci was the first to report this chiral epoxidation using (+)-isopinocamphone (**250**) as a catalyst to convert (*E*)- β -methylstyrene to epoxide **252**, but in only about 12% ee (1*R*,2*R*).³⁵⁰



There are many examples that use $Oxone^{\text{(B)}}$ in conjunction with chiral ketones other than **250** for the enantioselective epoxidation of alkenes, and with high %ee. Yang and co-workers used a C₂-symmetric biaryl ketone that gave highly enantioselective oxidations.³⁵¹ Denmark and Matsuhashi employed chiral fluoro ketones with good chiral efficiency for asymmetric epoxidation.³⁵² This area of research is clearly growing in importance as an alternative to the titanium-based and manganese-salen-based oxidations.

3.5. CONVERSION OF ALKENES TO DIOLS (C=C \rightarrow CHOH-CHOH)

Several reagents react with alkenes to generate 1,2-diols (dihydroxylation).³⁵³ 1,2-Diols and

- 348. Inoue, M.; Lee, N.; Kasuya, S.; Sato, T.; Hirama, M.; Moriyama, M.; Fukuyama, Y.J. Org. Chem. 2007, 72, 3065.
- 349. (a) Frohn, M.; Shi, Y. Synthesis 2000, 1979; (b) Reference 346d.
- 350. (a) Curci, R.; D'Accolti, L.; Fiorentino, M.; Rosa, A. Tetrahedron Lett. 1995, 36, 5831; (b) Curci, R.; Fiorentino, M.; Serio, M.R. J. Chem. Soc. Chem. Commun. 1984, 155.
- (a) Yang, D.; Yip, Y.-C.; Tang, M.W.; Wong, M.-K.; Zheng, J.-H.; Cheung, K.-K.; *J. Am. Chem. Soc.* 1996, 118, 491; (b) Yang, D.; Wang, X.-C.; Wong, M.-K.; Yip, Y.-C.; Tang, M.-W. J. Am. Chem. Soc. 1996, 118, 11311.
- 352. Denmark, S.E.; Matsuhashi, H. J. Org. Chem. 2002, 67, 3479.
- 353. Reference 20, pp 996-1003.

^{347. (}a) Frohn, M.; Wang, Z.-X.; Shi, Y. J Org. Chem. 1998, 63, 6425; (b) Baumstark, A.L.; Harden Jr., D.B., J. Org. Chem. 1993, 58, 7615; (c) Baumstark, A.L.; Vasquez, P.C. J. Org. Chem. 1988, 53, 3437; (d) Murray, R.W.; Jeyaraman, R. J. Org. Chem. 1985, 50, 2847.

polyols containing several hydroxyl moieties are important structural features of many natural products. 1,2-Diols are usually formed by the syn-addition of manganese or osmium reagents to an alkene. Mechanistically, these are syn- dipolar additions and will be discussed in section 11.11, but a cursory introduction will be given here. Potassium permanganate and osmium tetroxide are the most common reagents used to prepare 1,2-diols, and both reagents react with alkenes in this manner. An alternative route to 1,2-diols is available using silver salts of carboxylic acids will conclude this section.

3.5.A. Dihydroxylation with Potassium Permanganate

Permanganate (MnO_4^-) is a powerful oxidizing agent in basic, acidic and neutral media. In acidic solution, the reduction potential is 1.679 V or 1.491 V, but it is 0.588 V in basic solution according to the following reactions.¹⁷

 $MnO_4^- + 4 H^+ + 3 e^- \rightarrow MnO_2 + 2 H_2O$ 1.679 V

 $MnO_4^- + 8 H^+ + 5 e^- \rightarrow Mn^{2+} + 4 H_2O$ 1.491 V

$$MnO_4^- + 2 H_2O + 3 e^- \rightarrow MnO_2 + 4 HO^-$$
 0.588 V

In this section, permanganate [principally potassium permanganate ($KMnO_4$)] will be used to oxidize alkenes to 1,2-diols. Permanganate (MnO₄⁻, **253**) is a 1,3-dipolar molecule (δ^+ O and O⁻). An alkene will donate electrons to the electrophilic oxygen and form a C–O bond, and as the π -bond (O=Mn) breaks positive character develops on the other carbon. Subsequent attack by the negative oxygen of the dipolar molecule forms a ring (see 254). It is likely that this is a concerted process, controlled by the frontier orbital energies of the alkene and the dipole (see sec. 11.2, 11.11.A). Formation of cyclic manganate ester with a cis geometry for the two C-O bond in 254³⁵⁴ is accompanied by reduction of Mn(VII) to Mn(VI).³⁵⁴ Aqueous hydroxide leads to decomposition of the manganate ester 254 to generate a 1,2-diol (256), via stepwise cleavage of the Mn-O bonds (see 255), and the overall reaction is an oxidation of the alkene. The hydroxide ion attacks manganese in 254, rather than carbon, to form 255, so the stereochemistry in 254 is retained. Subsequent reaction with water and additional hydroxide liberates the cis- diol and the Mn(V) byproduct, which disproportionates to Mn(VII) [MnO₄⁻] and Mn(IV) [usually MnO₂]. The cis geometry of the oxygen atoms is fixed at the time of the dipolar addition, so the timing for C-O bond formation must be close if not concerted (sec. 11.11.A).³⁵⁵ Reaction of hydroxide at manganese rather than carbon leads to retention of the cis- stereochemistry.

^{354. (}a) Stewart, R. in Oxidation in Organic Chemistry, Wiberg, K.B. (Ed.), Academic Press, New York, 1965, chapter 1; (b) Wiberg, K.B.; Saegebarth, K.A. J. Am. Chem. Soc. 1957, 79, 2822; (c) Wagner, G. J. Russ. Phys. Chem. Soc. 1895, 27, 219; (d) Böeseken, J. Rec. Trav. Chim. 1928, 47, 683.

^{355.} Foradiscussion that establishes the [3+2]-mechanism, see Houk, K.N.; Strassner, T.J. Org. Chem. 1999, 64,800.

Permanganate reacts with an alkene in an exothermic process.³⁵⁶ This oxidation with KMnO₄ is compatible with several solvents (aqueous EtOH, acetone, *t*-BuOH) under acidic, basic or neutral conditions.³⁵⁷ Permanganate oxidation to the diol usually requires dilute conditions, since vigorous conditions (75°C, 0.2 M KOH) can lead to extensive carbon-carbon bond cleavage³⁵⁸ (sec. 3.7). In neutral media (and very low hydroxide concentration) large quantities of α -hydroxy ketone (ketols such as **258**) can be formed.³⁵⁹ Under these conditions the alkene reacts with permanganate to generate **255**, with Mn⁶⁺ as the byproduct. Aqueous hydrolysis generates **257** before hydroxide can attack manganese a second time, leading to the ketol and MnO₂. If strongly basic conditions are used to decompose **255**, the diol is the major product. Henbest showed that the presence of electron-withdrawing groups diminish the rate of diol formation and promoted the formation of diketones and cleavage products.³⁶⁰



Swern showed that the permanganate oxidation of oleic acid (**259**) was pH dependent. Earlier, Lapworth and Mottram oxidized oleic acid to 9,10-dihydroxy stearic acid (**260**)³⁶¹ in essentially quantitative yield by what might be considered standard conditions for hydroxylation: 0.1% oleic acid, no more than 1% KMnO₄, short reaction time (5 min), slight excess of alkali and a reaction temperature of 0-10°C.³⁶¹ Swern found that reaction of **259** with potassium permanganate and sodium hydroxide without pH control gave 45% of a mixture of 9-keto-10-hydroxystearic acid (**261**) and 10-keto-9-hydroxystearic acid (**262**), along with 30% of **260**.³⁶² If the pH of the reaction medium was controlled to pH 9-9.5 (by addition of sulfuric acid to the hydroxide solution), a 45% yield of a mixture of **261** and **262** was produced along with 20% of **260**.

356. Reference 42, p 6.

- 358. Hill, J.W.; McEwen, W.L. Org. Synth. Coll. Vol. 2 1943, 53.
- 359. (a) Reference 16a, pp 42; (b) Snyder, C.H. J. Chem. Educ. 1966, 43, 141.
- 360. Henbest, H.B.; Jackson, W.R.; Robb, B.C.G. J. Chem. Soc. B 1966, 803.
- 361. Lapworth, A.; Mottram, E.N. J. Chem. Soc. 1925, 1628.
- 362. Coleman, J.E.; Ricciuti, C.; Swern, D. J. Am. Chem. Soc. 1956, 78, 5342.

^{357.} Reference 42, p 7.

The ability to generate cis- diols stereoselectively is important in synthesis, where the ability to position functional groups with complete control is essential. In a synthesis of 21-fluoroprogestin-16,17-dioxolane as a high-affinity ligand for PET imaging of the progesterone receptor by Katzenellenbogen and co-workers,³⁶³ reaction of keto-acetate **263** with potassium permanganate in acetone, gave diol **264** in 85% yield. Note that dihydroxylation occurred exclusively from the bottom face of the molecule.



Potassium permanganate oxidation in the presence of phase transfer catalysts permits nonaqueous solvents such as dichloromethane to be used, which generally leads to an increase in yield of the oxidation products.³⁶⁴ A solution of dichloromethane and aqueous sodium hydroxide (+ alkene) uses a phase transfer agent such benzyltriethylammonium chloride to solubilize the reactants.³⁶⁵ When potassium permanganate was added to this mixture, oxidation of *cis*cyclooctene to *cis*-1,2-cyclooctanediol was observed in significantly higher yields than could be obtained under standard permanganate oxidation conditions.³⁶⁶

3.5.B. Dihydroxylation with Osmium Tetroxide

Osmium tetroxide (OsO₄) had a relatively high reduction potential (0.85 V) in acidic media, with OsO₄ being reduced to osmium metal.¹⁷

$$OsO_4 + 8 H^+ + 8 e^- \rightarrow Os + 4 H_2O$$
 0.85 V

For applications to organic chemistry, osmium tetroxide is most often used in neutral, aqueous media and the primary use is for the conversion of alkenes to 1,2-diols.

3.5.B.i. Dihydroxylation of Alkenes. Criegee found that osmium tetroxide (265) is reduced by alkenes to give the cis-diol, via an intermediate osmium complex that must be decomposed.³⁶⁷

^{363.} Vijaykumar, D.; Mao, W.; Kirschbaum, K.S.; Katzenellenbogen, J.A. J. Org. Chem. 2002, 67, 4904.

^{364. (}a) Okimoto, T.; Swern, D. J. Am. Oil Chem. Soc. 1977, 54, 867A; (b) Foglia, T.A.; Barr, P.A.; (c) Malloy, A.J. Ibid. 1977, 54, 858A.

^{365.} Reference 233a, p 84.

^{366.} Weber, W.P.; Shepherd, J.P. Tetrahedron Lett. 1972, 4907.

^{367. (}a) Criegee, R.; Marchand, B.; Wannowius, H. Annalen 1942, 550, 99; (b) Criegee, R. Ibid. 1936, 522, 75.

Osmium tetroxide vapors are poisonous and result in damage to the respiratory tract and temporary damage to the eyes.³⁶⁸ Use OsO_4 powder only in a well-ventilated hood with <u>extreme</u> caution.

In the absence of tertiary amines, osmium tetroxide reacts with alkenes via 1,3-dipolar addition to generate a monomeric Os(VI) ester such as **266**,³⁶⁹ where L is a **ligand** (a solvent molecule or an added substrate such as pyridine). A reducing agent is usually added to drive the reaction to the cis-diol by reducing Os(VI) to osmium metal, preventing reformation of the ester.³⁶⁸ When the reaction is done in the presence of a base such a pyridine, an ester complex like **267** is formed by coordination with two equivalents of the ligand (pyridine). Complexes such as **267** can sometimes be isolated.³⁶⁹ In most osmylation reactions of alkenes, the osmium ester is not isolated but decomposed with a reducing agent, producing the cis-1,2-diol. A variety of reagents can be used to decompose the osmium ester, including bisulfite ion in pyridine,³⁷⁰ sulfite, or bisulfite in aqueous ethanol,^{371,372,367} mannitol in alkaline solution,³⁶⁶ or potassium chlorate (KClO₃) under acidic conditions.³⁶⁶



Sharpless et al proposed an alternative mechanism.³⁷³ Octahedral osmate esters (generated directly by [3+2]-cycloaddition) are stable and isolable, but there would be severe angle strain in the initial tetrahedral metallocycle due to the long (ca. 2.2 A) osmium-oxygen bonds.³⁷⁴ A four-membered intermediate should be substantially less strained since the long Os–C and Os–O bonds would have the effect of relieving the angle strain in the four-membered ring.³⁷³ Sharpless et al. proposed that hydroxylation proceeds by a four-membered organoosmium intermediate, where coordination of a ligand (e.g., pyridine) would produce the octahedral complex and trigger reductive insertion of the Os–C bond into an oxo group yielding the osmium(V1) ester. This intermediate could react reversibly with additional ligand to give

- 372. Vyas, D.M.; Hay, G.W. Can. J. Chem. 1975, 53, 1362.
- 373. Sharpless, K.B.; Teranishi, A.Y.; Bäckvall, J.E. J. Am. Chem. Soc. 1977, 99, 3120.

^{368.} Reference 42, p 11.

^{369. (}a) Reference 233a, pp 75-76; (b) Schröder., M. Chem. Rev. 1980, 80, 187.

^{370.} Baran, J.S. J. Org. Chem. 1960, 25, 257.

^{371.} Barton, D.H.R.; Eland, D. J. Chem. Soc. 1956, 2085.

 ⁽a) Conn, J.F.; Kim, J.J.; Suddath, F.L.; Blattmann, P.; Rich, A. J. Am. Chem. Soc. 1974, 96, 7152; (b) Collin, R.; Jones, J.; Griffith, W.P. J. Chem. Soc. Dalton Trans., 1974, 1094; (c) Collin, R.; Griffith, W.P.; Phillips, F.L.; Skapski, A.C. Biochim. Biophys. Acta 1973, 320, 745; (d) Ibid. 1974, 354, 152.

266. Sharpless pointed out,³⁷³ however, that objections to the [3+2]-mechanism are removed if one invokes prior coordination of the nucleophile (the ligand, L) to OsO₄, where [3+2]-cycloaddition could proceed directly to the five coordinate ester.

An osmate complex is formed in the reaction, which can be decomposed in aqueous or alcoholic solution, but the hydrolysis is reversible. The relatively bulky osmium complex is sterically demanding and osmylation generally involves reaction at the less hindered face of an alkene. In a synthesis of himandrine by Mander and co-workers,³⁷⁵ catalytic dihydroxylation (see below) of **268** failed, but oxidation with a stoichiometric quantity of osmium tetroxide gave the isomeric triol **269** in about 75% yield. Dihydroxylation occurred from the less sterically hindered top (exo) face of **268**.



When stoichiometric amounts of osmium tetroxide are required, applications are often limited to small-scale reactions due to the toxicity and expense.³⁷⁶ Procedures have been developed where osmium tetroxide is used as a catalyst,³⁷⁷ greatly expanding the utility of this reagent. Effective catalysts in this reaction are metal chlorates, hydrogen peroxide, *t*-BuOOH and amine *N*-oxides. Tertiary amine *N*-oxides such as NMO (*N*-methylmorpholine *N*-oxide) are effective catalysts developed by Van Rheenan et al.³⁷⁸ These reagents are both a catalyst for the reaction and also as agents to decompose the osmylate ester. Osmylations with NMO can be accomplished with about 1 mol % of OsO₄ at ambient temperatures. This procedure is superior to other syn-hydroxylation procedures since only small amounts of osmium tetroxide are used.³⁷⁹

Relatively unsubstituted alkenes react quickly, but the oxidation failed with several highly substituted alkenes.³⁸⁰ Note that a trisubstituted alkene was successfully oxidized using this reagent.³⁸¹ The use of trimethylamine *N*-oxide often gives better results than NMO in reactions with hindered alkenes.³⁸² The reaction is usually run in aqueous acetone, THF or

^{375.} O'Connor, P.D.; Mander, L.N.; McLachlan, M.M.W. Org. Lett. 2004, 6, 703.

^{376.} Reference 233a, p 75.

^{377. (}a) Reference 233a, pp 77-84; (b) Reference 42, pp 13-14.

^{378. (}a) Van Rheenen, V.; Kelly, R.C.; Cha, D.Y. *Tetrahedron Lett.* 1976, 1973; (b) Van Rheenen, V.; Cha, D.Y.; Hartley, W.M. Org. Synth. Coll. Vol. 6 1988, 342.

^{379.} Reference 233a, p 81.

^{380.} Akashi, K.; Palermo, R.E.; Sharpless, K.B. J. Org. Chem. 1978, 43, 2063.

^{381. (}a) Larsen, S.D.; Monti, S.A. J. Am. Chem. Soc. 1977, 99, 8015; (b) Schneider, W.P.; McIntosh, A.V. U.S. Patent, 2 769 824 1956 [Chem. Abstr. 51: 8822, 1957].

^{382.} Ray, R.; Matteson, D.S. Tetrahedron Lett. 1980, 21, 449.
tert-butanol as a one or two-phase reaction. Riera and co-workers used NMO in a synthesis of deoxymannojirimycin, to convert **268** to **269** in 96% yield (12/1 dr).³⁸³ Alkenes bearing electron-withdrawing groups react more slowly with OsO₄.^{360,384}



As with permanganate oxidations, α -hydroxy ketones can be formed as side products. In some cases, structural features make the osmium complex relatively unstable. In an aqueous medium it can react with water to give a hydroxy-hydrate, which is then converted to an α -keto alcohol. Sharpless et al. developed a procedure that used *tert*-butyl hydroperoxide with a catalytic amount of osmium tetroxide,³⁸⁵ in the presence of tetraethylammonium hydroxide (Et₄N⁺ OH⁻). The procedure gave improved yields of the cis-diol and a little α -hydroxyketone, as shown in the conversion of oct-(4*E*)-ene to a mixture of **270** and **271** in 73% yield. This method is more reliable for oxidation of tri- and tetrasubstituted alkenes than the Van Rheenan procedure. The reaction was not suitable for base sensitive alkenes, but later work showed that changing the solvent to acetone allowed the use of tetraethylammonium acetate (Et₄NOAc)³⁸⁶ for the hydroxylation of sensitive alkenes such as ethyl crotonate.





^{383.} Martín, R.; Murruzzu, C.; Pericàs, M.A.; Riera, A. J. Org. Chem. 2005, 70, 2325.

^{384.} Ferretti, A.; Tesi, G. J. Chem. Soc. 1965, 5203.

^{385.} Sharpless, K.B.; Akashi, K. J. Am. Chem. Soc. 1976, 98, 1986.

^{386.} Akashi, K.; Palermo, R.E.; Sharpless, K.B. J. Org. Chem. 1978, 43, 2063.

MOLECULAR MODELING: Oxidation of a Conjugated Diene, con't.

Assignment of which double bond is likely to be oxidized as well as the stereochemistry of attack can be accomplished using a local ionization potential map. This colors an electron density surface that indicates overall molecular size and shape with the value of the energy required to remove an electron from a region on the surface. By convention, regions where ionization is difficult are colored "blue", while regions where it is easy are colored "red". The more red a region associated with a carboncarbon double bond, the more nucleophilic the bond. The more red the face of a particular bond, the more likely the face will approach an electrophilic reagent. Thus, a local ionization potential map makes it possible to identify regions that are nucleophilic and will donate electrons to an electron acceptor (colored red) from those most likely to accept electrons from a donor (colored blue).

Examine the local ionization potential map for this diene. It is depicted as a transparent model, allowing the underlying structures to be seen. You can switch to a solid model, allowing the maps to be seen more easily, by *clicking* on the map and then selecting *Solid* for the **Style** menu at the bottom of the screen.) For which double bond is the local ionization potential smaller? You can get the value of the local ionization on a particular region of the surface by *clicking* on that region. It will be displayed at the bottom of the screen. For which face, *syn* or *anti* to the OSiMe₂t-Bu, is the local ionization potential smaller? Does this lead to the observed oxidation product? According to the local ionization potential map, are any other sites on the diene likely to be competitive? If so, identify the product(s) that would result.

3.5.B.ii. Sharpless Asymmetric Dihydroxylation. Although osmylation is an attractive method for the conversion of alkenes to 1,2-diols, the reaction generates racemic products. Sharpless³⁸⁷ solved this problem by adding a chiral substrate to the osmylation reagents, with the goal of generating a chiral osmate intermediate. Cinchona alkaloids, especially esters of dihydroquinidines such as 272 and 273 were very effective. The % ee of the diol product is good-to-excellent with a wide range of alkenes in what is called the Sharpless asymmetric dihydroxylation.³⁸⁸ The chiral alkaloid forms a complex with the osmium and the alkene, directing attack from the *opposite* enantioface of the alkene.³⁸⁷ The cis-addition imposed by the cyclic osmium intermediate is very important in reactions of acyclic alkenes, because the two hydroxyl moieties in the product aree syn-, making the reaction highly diastereoselective. This selectivity is also dependent on the geometry of the alkene precursor, and high diastereoselectivity is obtained only with regiochemically pure alkenes. This selectivity is illustrated by the reaction of trans-stilbene with OsO4 and NMO, which gave the diol 274 with 99% ee in the presence of 272. In general, the %ee in the asymmetric dihydroxylation procedure were lower than those observed in the asymmetric epoxidation reaction (sec. 3.4.D). Ionic liquids such as 1,3-dialkylimidazolium compounds have been used as a medium for Sharpless asymmetric dihydroxylation, using a recoverable and reusable osmium-ligand.³⁸⁹

^{387. (}a) Jacobsen, E.N.; Markó, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. J. Am. Chem. Soc. 1988, 110, 1968; (b) Hentges, S.G.; Sharpless, K.B. Ibid. 1980, 102, 4263.

^{388.} The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-85.

^{389.} Branco, L.C.; Afonso, C.A.M. J. Org. Chem. 2004, 69, 4381.



The source of enantioselectivity can be discerned from the structure of the osmium complex.³⁹⁰ An X-ray crystal structure of the OsO_4 complex of (dimethylcarbamoyl) dihydroquinidine (275) has been published.³⁹¹ Using 275 as a guide, the osmium complex of stilbene can be



[Reprinted with permission from Svendsen, J.S.; Markó, I.; Jacobsen, E.N.; Pulla Rao, Ch.; Bott, S.; Sharpless, K.B. *J. Org. Chem.* **1989**, *54*, 2263. Copyright © 1989 American Chemical Society.] Structure drawn using Spartan software by Wavefunction, Inc. Hydrogen atoms omitted for clarity.

represented as **276** (the *p*-methoxy ester was used in this case), which may not be the active complex, but it illustrates how selectivity arises in the reaction. Stilbene coordinates with osmium in a manner that minimizes any interaction of the phenyl groups with the azabicyclo[2.2.2] octane moiety and/or with the methylquinoline ring. As seen in **276**, O1 is significantly more hindered than O2. The phenyl rings of the stilbene molecule are oriented so that those rings are away from O2 and the azabicyclooctane ring. If stilbene binds in this way, the threo (syn) isomer (**274**) will be the major diol product. The chirality of the Cinchona alkaloid is important since it provides facial selectivity for complexation of the alkene and control of orientation via the steric interactions described above. Figure 3.2^{330} is a graphic similar to Figure 3.1 (which showed a model for Sharpless asymmetric epoxidation) to illustrate the facial. If the alkene is oriented as in Figure 3.2, using the naturally-occuring dihydroquinidine ester forces delivery of the hydroxyls from the top face. Conversely, dihydroquinoline esters deliver hydroxyls from the bottom face. Highest % ee values (70-90%) are obtained with trans-1,2-disubstituted

For an *ab initio* approach to this mechanism, see Veldkamp, A.; Frenking, G. J. Am. Chem. Soc. 1994, 116, 4937.

^{391.} Svendsen, J.S.; Markó, I.; Jacobsen, E.N.; Pulla Rao, Ch.; Bott, S.; Sharpless, K.B. J. Org. Chem. 1989, 54, 2263.

alkenes,³³⁰ and the lowest are obtained with cis-1,2-disubstituted alkenes.²⁹⁴ Trisubstituted and monosubstituted alkenes show greater variation in asymmetric induction (30-80% ee and 25-60% ee, respectively).³³⁰



New catalysts are available for this reaction that improve the efficiency and ease of use. Two phthalazine derivatives,³⁹² (DHQD)₂PHAL (**277**) and (DHQ)₂PHAL (**278**) have been used in conjunction with an osmium reagent, resulting in two commercial catalysts, AD-mix- β^{393} (using **277**) and AD-mix- α^{393} (using **278**). The abbreviations shown here refer to the reagents used to make each catalyst. Catalyst **277** is prepared from dihydroquinidine (DHQD) and 1,4-dichlorophthalazine (PHAL), and **278** is prepared from dihydroquinine (DHQ) and PHAL. The actual oxidizing medium labeled AD-mix α or β - uses **278** or **277**, respectively, mixed with potassium osmate [K₂OsO₂(OH)₄], powdered K₃Fe(CN)₆, and powdered K₂CO₃ in an aqueous solvent mixture.³⁹² These mixes have become standard catalysts for dihydroxylation. Sharpless introduced a model, shown in Figure 3.3,³⁹² to predict the enantioselectivity of each catalyst. With the R_L, R_M, and R_s substituents of the alkene arranged as shown, the AD-mix- β catalyst gives dihydroxylation from the top, whereas the AD-mix- α catalyst gives dihydroxylation from the top.



^{392.} Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. J. Org. Chem. 1992, 57, 2768.

^{393.} A trademark of the Aldrich Chemical Co., Inc.



Figure 3.3. Facial selectivity in asymmetric dihydroxylation using AD-mix-α and AD-mix-β. [Reprinted with permission from Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768. Copyright © 1992 American Chemical Society.]

In a synthetic example, McDonald and Fei used AD-mix- β^{393} to convert **279** to **280** in 89% yield and and enantiomeric ratio of 13:1, in a synthesis of altromycin aglycone.³⁹⁴ Similarly, Hecht and co-workers reacted AD-mix- α^{393} with **281**, as part of synthesis of (+)-myristinin A³⁹⁵ to give an 84% yield of diol **282**.



3.5.C. The Prévost Reaction

An alternative route to 1,2-diols reacts alkenes with a mixture of silver carboxylate and iodine rather than with a peroxide. Prévost found that silver benzoate and iodide converted styrene to 1,2-dibenzoate **283**, which could be saponified to the 1,2-diol.^{396a,358} The transformation is



^{394.} Fei, Z.B.; McDonald, F.E. Org. Lett. 2005, 7, 3617.

^{395.} Maloney, D.J.; Deng, J.-Z.; Starck, S.R.; Gao, Z.; Hecht, S.M. J. Am. Chem. Soc. 2005, 127, 4140.

^{396. (}a) Prévost, C. Compt. Rend, 1933, 196, 1129; (b) Wilson, C.V. Org. React., 1957, 9, 332 (see p 350).

called the **Prévost reaction**.^{396,397} This reaction is related to the **Hunsdiecker reaction**.^{396b,398} (described in sec. 2.8.A). Birkenbach et al. reported a similar reaction of alkenes and silver carboxylates in which cyclohexene was treated with silver acetate and iodide to give 2-iodocyclohexanol.³⁹⁹ Brunel had earlier reported a related reaction using iodine and mercuric acetate.⁴⁰⁰ The Prévost reaction is illustrated using cyclohexene, and water is not involved in the transformation. Initial formation of an iodonium salt from reaction of cyclohexene and iodine is followed by reaction with silver benzoate to give **284a**.³⁹⁶ Attack by a second molecule of benzoate gives the trans diacetate, **287a**, presumably via a cyclic species such as **285a**, which is opened by benzoate to give the trans diester. Saponification generates the trans-diol (**288**). The Prévost reaction therefore generates trans diols, in contrast to permanganate and osmium hydroxylation reactions, which give cis diols. Alternatively, water can attack **285** to give **286**, which in turn is attacked by the carboxylate anion to give **287**. An example is the conversion of **289** to **290** in 94% yield.⁴⁰¹



As mentioned, the Prévost reaction proceeds via initial formation of an iodonium salt that is opened by the silver carboxylate. Winstein studied reactions of silver acetate and bromine with alkenes, and showed that initial formation of the bromonium ion was followed by

^{397.} The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-76.

^{398.} The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-47.

^{399.} Birkenbach, L.; Goubeau, J.; Berninger, E. Berichte, 1932, 65, 1339.

^{400.} Brunel, L. Bull. Soc. Chim. Fr. 1905, 33, 382.

^{401. (}a) Harvey, R.G.; Fu, P.P.; Cortez, C.; Pataki, J. *Tetrahedron Lett.* 1977, 3533; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd Ed.*, Wiley, New York, 2005, pp 338-339.

formation of a bromoacetate (284b), which is analogous to 284a.⁴⁰² In aqueous media, attack by the neighboring acetate generates an oxonium salt (285b) that reacts with water to form 286b. Reaction with additional silver acetate gives the final product, a trans 1,2-diester 287b. The presence of water in the reaction apparently changed its course from an intermolecular displacement of 285, which gave the trans-product, to attack by water with ring opening, which preserved the cis stereochemistry. This is called the **Woodward modification**⁴⁰³ of the Prévost reaction and gives the cis-diol rather than the trans-diol. Woodward used this modification in the conversion of 291 to the cis acetate, which was saponified to give diol 292 in 65% overall yield.⁴⁰³



An alternative route to trans diols is available by hydrolysis of epoxides. Reaction of cyclohexene with mcpba gives cyclohexene oxide and hydrolysis (acid or base) gives *trans*-1,2-cyclohexanediol.

The functional group transforms for all of the hydroxylation reactions in this section are



3.5.D. Dihydroxylation of Aromatic Rings

Enzymatic transformations of organic molecules are an increasingly important source of chiral, nonracemic products. Transformations in previous sections focused on oxidation of the π bonds in alkenes, but these reagents generally do not work with aromatic rings. It is possible to convert one π -bond of an aromatic ring into racemic or chiral, nonracemic cyclohexadiene 1,2-diols using enzymes associated with the organism *Pseudomonas putida*.⁴⁰⁴,⁴⁰⁵ Early work by Gibson et al. established that racemic **293** could be formed in good to moderate yield by

^{402.} Winstein, S.; Buckles, R.E. J. Am. Chem. Soc. 1942, 64, 2787, 2780.

^{403. (}a) Woodward, R.B.; Brutcher, Jr., F.V. J. Am. Chem. Soc. 1958, 80, 209; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-103. Brimble found that iodo-acetates can be isolated in some cases, as found in (c) Brimble, M.A.; Nairn, M.R. J. Org. Chem. 1996, 61, 4801.

^{404. (}a) Brown, S.M. in Organic Synthesis: Theory and Practice, T. Hudlicky (Ed.), JAI Press, Greenich, CT., 1993, Vol. 2, p 113; (b) Carless, H.A.J. Tetrahedron Asymmetry 1992, 3, 795; (c) Widdowson, D.A.; Ribbons, D.A.; Thomas, S.D. Janssenchimica Acta 1990, 8, 3.

^{405.} For recent reviews, see (a) Hudlicky, T.; Gonzalez, D.; Gibson, D.T. *Aldrichimica Acta* 1999, 32, 35; (b) Hudlicky, T.; Abboud, K.A.; Entwistle, D.A.; Fan, R.; Maurya, R.; Thorpe, A.J.; Bolonick, J.; Myers, B. *Synthesis* 1996, 897. Also see, Reference 20, p 978.

exposure of benzene to *P. putida*,⁴⁰⁶ based on earlier work by Marr and Stone⁴⁰⁷ and by Walker and Wiltshire.⁴⁰⁸ In even earlier work, Ballard et al. had postulated **293** as an intermediate in the oxygen assisted oxidation of benzene derivatives in the presence of *P. putida*.⁴⁰⁹



Gibson showed that this transformation is not limited to benzene. The reaction can be generalized to give products such as **294**. In specific cases chlorobenzene gave **295**,⁴¹⁰ bromobenzene gave **296**, 4-chlorotoluene gave **297**⁴¹¹ and toluene gave **298**,⁴¹¹ all with excellent asymmetric induction since the aromatic ring contains a substituent and introduction of the hydroxyl groups generates a chiral molecule. In one sense, this oxidation belongs in section 2.11, which described various transformations of benzene derivatives. Since this reaction formally involves the conversion of a π bond in a benzene ring to a cis diol, however, it is placed in this section for the sake of continuity.



Recently, this transformation has been used in a variety of interesting syntheses, particularly by Hudlicky and by Ley. Ley showed that **293** could be converted to conduritol F (**299**) in four steps (25% overall yield).⁴¹² Carless and Hensley also prepared conduritol A and D using similar methodology.⁴¹³ In other work, Ley et al. converted **295** to myoinositol-1,4,5-triphosphate (IP₃)⁴¹⁴ and **293** to pinitol, an antidiabetic agent.⁴¹⁵ Hudlicky et al. prepared (+)-pinitol in an enantiodivergent synthesis that used the chiral derivative **296** as a starting material.⁴¹⁶ This

- 406. Gibson, D.T.; Koch, J.R.; Kallio, R.E. Biochemistry 1968, 7, 2653.
- 407. Marr, E.K.; Stone, R.W. J. Bacteriol. 1961, 81, 425.
- 408. Walker, N.; Wiltdshire, G.H. J. Gen. Microbiol. 1953, 8, 273.
- 409. Ballard, D.G.H.; Courtis, A.; Shirley, I.M.; Taylor, S.C. J. Chem. Soc. Chem. Commun. 1983, 954.
- 410. Gibson, D.T.; Koch, J.R.; Schuld, C.L.; Kallio, R.E. Biochemistry 1968, 7, 3795.
- 411. Gibson, D.T.; Hensley, M.; Yoshioka, H.; Mabry, T.J. Biochemistry 1970, 9, 1626.
- 412. Ley, S.V.; Redgrave, A.J. Synlett 1990, 393.
- 413. Carless, H.A.J.; Oak, O.Z. Tetrahedron Lett. 1989, 30, 1719.
- 414. Ley, S.V.; Sternfeld, F. Tetrahedron Lett. 1988, 29, 5305.
- 415. Ley, S.V.; Sternfeld, F.; Taylor, S. Tetrahedron Lett. 1987, 28, 225.
- 416. Hudlicky, T.; Price, J.D.; Rulin, F.; Tsunoda, T. J. Am. Chem. Soc. 1990, 112, 9439.

latter example illustrates the true power of this method, since chiral nonracemic synthetic targets can be produced from readily available starting materials.



A wide range of chiral nonracemic targets can be prepared using aromatic rings as precursors to diols. Hudlicky prepared **295** in >99.9% ee,⁴¹⁷ and used this diol to synthesize 2,3-isopropylidene (*L*)-ribose γ -lactone (**300**) in four steps (18% overall yield).^{417,418} *O*-Linked diinositols have also been prepared, using **285** as the chiral building block.⁴¹⁹ Diols such as **295** and **296** are useful in a variety of syntheses. Diol **296**⁴²⁰ was used as the diene partner in a Diels-Alder reaction (sec. 11.4) for the synthesis of amino cyclitols. After oxidation of styrene with *P. putida*, the resulting diol was used to synthesize zeylena via a Diels-Alder reaction.⁴²¹ The methyl derivative (**297**) was used for the preparation of terpene and prostanoid synthons.⁴²² Johnson and Penning used **295** as a precursor for the synthesis of prostaglandin PGE₂, resolving the starting material to provide the asymmetric precursor.⁴²³



The synthesis of nitrogen-containing natural products is also possible via this route. Hudlicky and co-workers prepared the bicyclic alkaloid (+)-kifunensine, for example, from **295**.⁴²⁴ More complex molecules can also be prepared, as illustrated by the conversion of **296** into

422. Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L.D. J. Am. Chem. Soc. 1988, 110, 4735.

424. Rouden, J.; Hudlicky, T. J. Chem. Soc. Perkin Trans. 1 1993, 1095.

^{417.} Hudlicky, T.; Price, J.D. Synlett 1990, 159.

^{418.} Hudlicky, T.; Luna, H.; Price, J.D.; Rulin, F. Tetrahedron Lett. 1989, 30, 4053.

^{419.} Paul, B.J.; Willis, J.; Martinot, T.A.; Ghiviriga, I.; Abboud, K.A. Hudlicky, T.J. Am. Chem. Soc. 2002, 124, 10416.

^{420.} Hudlicky, T.; Olivo, H.F. Tetrahedron Lett. 1991, 32, 6077.

^{421.} Hudlicky, T.; Seoane, G.; Pettus, T. J. Org. Chem. 1989, 54, 4239.

^{423.} Johnson, C.R.; Penning, T.D. J. Am. Chem. Soc. 1986, 108, 5655.

(+)-pancratistatin $(302)^{425}$ via 301. Banwell et al. reported an asymmetric synthesis of (-)-patchoulenone from 298 using this *P. putida*-mediated approach.⁴²⁶

The use of **295-298** as well as other diol derivatives derived from functionalized aromatic compounds is clearly an important method for the preparation of molecules that can be used in asymmetric synthesis. Enzymatic oxidation is an important source of diol starting materials that can be manipulated to form a variety of important natural products. This interesting oxidation leads to the functional group transform:



3.5.E. Aminohydroxylation

Asymmetric dihydroxylation of alkenes can be modified to synthesize amino alcohols,⁴²⁷ in what is known as **Sharpless asymmetric aminohydroxylation** (or **oxyamination**).⁴²⁸ When conjugated alkenes were treated with nitrogen-containing reagents in the presence of $(DHQ)_2PHAL$ (**278**), using what is effectively the AD-mix- α ,³⁹³ chiral, nonracemic amino alcohols were formed. The nitrogen sources include TsNClNa,⁴²⁸ MsNClNa,⁴²⁹ CbzNClNa,⁴³⁰ and BocBNClNa.⁴³¹ In a typical example treatment of cinnamate **303** with **378**, 4% K₂OsO₂(OH)₄ and MsNClNa in aqueous acetonitrile gave a 65% yield of **304** in 94% ee.^{427a} Boger and co-workers used this procedure in a synthesis of ramoplanin A2,⁴³² where **305** was converted to protected amino-alcohol **306** in 71% yield (99% ee).



^{425.} Tian, X.; Hudlicky, T.; Königsberger, K. J. Am. Chem. Soc. 1995, 117, 3643.

- 429. Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. Angew. Chem. Int. Ed. 1996, 35, 2810.
- 430. Li, G.; Angert, H.H.; Sharpless, K.B. Angew. Chem. Int. Ed. Engl, 1996, 35, 2813.
- 431. (a) Reddy, K.L.; Sharpless, K.B. J. Am. Chem. Soc, 1998, 120, 1207; (b) O'Brien, P.; Osborne, S.A.; Parker, D.D. J. Chem. Soc. Perkin Trans 1, 1998, 2519.
- 432. (a) Jiang, W.; Wanner, J.; Lee, R.J.; Bounaud, P.-Y.; Boger, D.L. J. Am. Chem. Soc. 2003, 125, 1877; (b) Boger, D. L.; Lee, R. J.; Bounaud, P.-Y.; Meier, P. J. Org. Chem. 2000, 65, 6770.

^{426.} Banwell, M.; McLeod, M. Chem. Commun. 1998, 1851.

^{427. (}a) O'Brien, P. Angew. Chem. Int. Ed. 1999, 38, 326; (b) Bodkin, J.A.; McLeod, M.D. J. Chem. Soc. Perkin Trans. 1 2002, 2733.

^{428. (}a) Li, K.B.; Chang, H.-T.; Sharpless, K.B. *Angew. Chem. Int. Ed.* **1996**, *35*, 451; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, **2006**, p ONR-86.

3.6. BAEYER-VILLIGER OXIDATION (RCOR' \rightarrow RCO₂R')

3.6.A. Peroxide Induced Baeyer-Villiger Oxidation

We have just seen that the π bond of an alkene reacts with peroxides. The π bond of a carbonyl group can also react with peroxides, but the reaction is accompanied by a rearrangement. In the most common application, ketones react with peroxyacids to give esters via a C \rightarrow O rearrangement known as the **Baeyer-Villiger reaction**.⁴³³ Both acid and base catalyzed mechanisms have been proposed. The acid catalysis mechanism⁴³⁴ proceeds via **307**,⁴³⁵ and base catalyzed reaction with hydrogen peroxide⁴³⁶ have proposed **308** as the key intermediate.⁴³⁵ A solid-state variation of this reaction has been reported in which peroxy acids supported on hexagonal mesoporous silica are used to induce the Baeyer-Villiger reaction.⁴³⁷



In all cases, an alkyl group migrates to the electrophilic oxygen with concomitant loss of the acyl or hydroxyl leaving group. Since hydroxyl is a poorer leaving group than acyl, the base-catalyzed reaction is "inferior to the peroxyacid route."⁴³⁸ With peroxyacids, the conversion of alkenes to epoxides can compete with the Baeyer-Villiger reaction. Ketones react with peroxyacids more slowly than do alkenes, usually requiring long reaction times, strong acid catalysts and highly reactive peroxyacids.⁴³⁹ As stated by Lewis, however, "this rate difference is not large with isolated carbon-carbon double bonds and Baeyer-Villiger oxidation can be competitive with epoxidation."⁴⁴⁰ Lewis illustrated this difference in reactivity in the oxidation of **309** with peroxyacetic acid, which gave a 44% yield of lactone **310** and no epoxide. Changing to hydrogen peroxide (benzonitrile was the solvent) led to epoxide **311** in 54% yield rather than the lactone. When an alkene and a carbonyl are present in the same molecule, the presence of an acid catalyst leads to preferential attack at the carbonyl. Selective epoxidation is best accomplished

- 434. Hawthorne, M.F.; Emmons, W.D. J. Am. Chem. Soc. 1958, 80, 6398.
- 435. Reference 254, p 237.
- 436. House, H.O.; Wasson, R.L. J. Org. Chem. 1957, 22, 1157.
- 437. Lambert, A.; Elings, J.A.; Macquarrie, D.J.; Carr, G.; Clark, J.H. Synlett 2000, 1052.
- 438. Reference 254, p 238.
- 439. Reference 433a, p 321.

⁽a) House, H.O. *Modern Synthetic Reactions*, 2nd Ed., Benjamin, Menlo Park, CA, *1972*, pp 306-307, 321-328; (b) Reference 254, p 237; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, *2006*, p ONR-4. Also see, Reference 20, p 1845.

^{440. (}a) Reference 254, p 241; (b) Payne, G.B. Tetrahedron 1962, 18, 763.



in a reaction medium that does not contain acid. The use of mcpba in an inert solvent at low temperature usually gives selective epoxidation.³⁷⁰ Silverstein and co-workers exploited this selectivity for the conversion of **312** to **313** in a synthesis of α -multistriatin.⁴⁴¹ Conjugated ketones react with mcpba to give mixtures of products, and steric hindrance can have a significant influence on the course of the reaction. Oxidation of 3-hydroxycholesten-4-en-6-ones, for example, gave mixtures of an epoxide and a lactone where proportions varied with the stereochemistry of the hydroxy group (α or β).⁴⁴² Glotter and co-workers concluded that for this system, the Baeyer-Villiger reaction was faster than epoxidation.⁴⁴²



Although most peroxyacids can be used in the Baeyer-Villiger reaction, trifluoroperoxyacetic acid⁴⁴³ is one of the more efficient reagents for this rearrangement. Such reactions are usually buffered with disodium phosphate (Na₂HPO₄)⁴⁴⁴ since the by-product of this reaction is the carboxylic acid precursor of the peroxyacid (sec. 3.4.C). Generation of a strong acid such as trifluoroacetic acid (from trifluoroperoxyacetic acid) may cause problems in an unbuffered reaction. In the generalized reaction of **314**, the final product is an ester (**315**) and CF₃COOH. The presence of both compounds in solution raises the possibility of transesterification reactions. Transesterification of **315** would give a trifluoroacetyl ester (**316**) and acid **317**.⁴⁴³ Addition of a buffer to the initial reaction minimizes transesterification and other acid catalyzed reactions. Typical buffers include disodium phosphate or the salt of the original acid (RCO₂⁻Na⁺ for example). In the case of **315**, CF₃CO₂⁻M⁺ or even sodium acetate might be a suitable as a buffer.

A useful synthetic example of the Baeyer-Villiger oxidation taken from Liebeskind and Zhang's synthesis of (–)-Bao Gong Teng A, in which methyl ketone **318** was converted to ester **319**

^{441.} Pearce, G.T.; Gore, W.E.; Silverstein. R.M. J. Org. Chem. 1976, 41, 2797.

^{442.} Mendelovici, M.; Glotter, E. J. Chem. Soc. Perkin Trans. 1 1992, 1735.

^{443.} Reference 433a, p 322.

^{444.} For an example, see Emmons, W.D.; Lucas, G.B. J. Am. Chem. Soc. 1965, 77, 2287.



in 75% yield using mcpba.⁴⁴⁵ Note that the larger group migrated in preference to the methyl group, which is characteristic of this reaction. When an unsymmetrical ketone such as **314** is treated with a peroxyacid, two esters are possible (**315** and/or **320**). Different groups (R and R¹ in **314**) will show different migratory aptitudes in the Baeyer-Villiger reaction. Both Lewis⁴⁴⁶,435 and House⁴⁴⁷ reported the migratory aptitude of alkyl groups (R) in **314** to be

$\begin{array}{l} \textit{tert-alkyl} > \textit{cyclohexyl} \approx 2^{\circ}\textit{ alkyl} \approx \textit{benzyl} \approx \textit{phenyl} > \\ \textit{vinylic}^{448,446} > 1^{\circ}\textit{ alkyl} > \textit{cyclopropyl} > \textit{methyl} \end{array}$	
$R^{O}_{R} R^{1}_{314}$	$ \xrightarrow{O}_{R} \xrightarrow{O}_{OR^{1}} + \xrightarrow{O}_{R} \xrightarrow{O}_{315} \xrightarrow{320} $

This migratory preference is clear in Fukuyama and co-worker's oxidation of **321** to **322** in >80% yield, taken from a synthesis of (+)-vinblastine.⁴⁴⁹ There may be some correlation between migratory ability and the ability of that group to stabilize a δ + charge, but as stated by House "this property, arising from the electron distribution in the migratory group, cannot be the only factor determining migratory aptitude".⁴⁵⁰ Electron-releasing groups on aromatic derivatives accelerate the rearrangement and electron-withdrawing groups slow it. Aryl groups generally migrate in preference to alkyl groups.⁴⁵¹ Although the reaction is usually selective, other products are formed and they can sometimes be difficult to separate.



- 445. Zhang, Y.; Liebeskind, L.S. J. Am. Chem. Soc. 2006, 128, 465.
- 446. (a)Reference254,p241;(b)Hawthorne,M.F.;Emmons,W.D.;McCallum,K.S.J.Am. Chem. Soc. 1958, 80, 6393.
- 447. Reference 433a, p 324.
- 448. Walton, H.M. J. Org. Chem. 1957, 22, 1161.
- 449. Yokowhima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. J. Am. Chem. Soc. 2002, 124, 2137.
- 450. Reference 433a, p 326.
- 451. (a) Reference 254, pp 241-242; (b) Friess, S.L.; Farnham, N. J. Am. Chem. Soc. 1950, 72, 5518.

Scandium triflate has been used in conjunction with mcpba to facilitate the Baeyer-Villiger rearrangement.⁴⁵² In a synthesis of (\pm) -*trans*-kumausyne by Philips and Chandler,⁴⁵³ bicyclic ketone **323** was converted to lactone **324** in 86% yield.

Simple dialkyl ketones are not easily oxidized by less reactive peroxyacids and usually require the more powerful trifluoroperoxyacetic acid.⁴⁵⁴ Since most groups migrate in preference to methyl, "the Baeyer-Villiger reaction of methyl ketones serves as a stereospecific source of optically active alcohols by way of the acetate"⁴⁵⁵ as seen in the conversion of **325** to **326** in 85% yield.⁴⁵⁶ This example also illustrates that the stereochemical integrity of the migratory group is retained, which appears to be a general phenomenon.⁴⁵⁷ Saponification of the ester product from the Baeyer-Villiger reaction is easily accomplished, leading to the alcohol and the interesting functional group transform (C–C=O \rightarrow C–OH) for acyclic ketones. Cyclic ketones (such as **309** and **321**) are more reactive than their acyclic counterparts and oxidation with a variety of peroxyacids leads to good yield of the corresponding lactone, as in the conversion of cyclopentanone to δ -valerolactone in 81% yield⁴⁵⁸ (also see 321 \rightarrow 322). Hydrolysis of the lactone leads to a ω -hydroxy acid but the facility of the ring opening depends on the size of the lactone ring. Aqueous hydrolysis is an equilibrium process that favors the closed ring in five-membered ring systems, but the open chain compound with seven-membered and higher lactones. The peroxyacid reaction⁴⁵⁹ should be buffered to prevent unwanted acid-catalyzed ring opening in such cases. Six-membered ring lactones are intermediate in stability between those just cited, and hydrolysis will usually give a mixture of the lactone and the open-chain acid. The migratory aptitude of the alkyl moieties in mono- and disubstituted cyclic ketones is the same as that observed with acyclic ketones.



Other carbonyl derivatives react with peroxyacids. 1,2-Diketones, o-quinones, and α -keto-

- 452. Kotsuki, H.; Arimura, K.; Araki, T.; Shinohara, T. Synlett 1999, 462.
- 453. Chandler, C.L.; Philips, A.J. Org. Lett. 2005, 7, 3493.
- 454. Reference 254, p 239.
- 455. Reference 254, p 242.
- 456. Baggiolini, E.G.; Iacobelli, J.A.; Hennessy, B.M.; Batcho, A.D.; Sereno, J.F.; Uskokovic', M.R. J. Org. Chem. 1986, 51, 3098
- 457. (a) Reference 254, p 237; (b) Mislow, K.; Brenner, J. J. Am. Chem. Soc. 1953, 75, 2318.
- 458. (a) Reference 433a, p 323; (b) Sager, W.F.; Duckworth, A. J. Am. Chem. Soc. 1955, 77, 188.
- (a) Friess, S.L. J. Am. Chem. Soc. 1949, 71, 2571; (b) Friess, S.L.; Frankenburg, R.E. Ibid. 1952, 74, 2679;
 (c) Mateos, J.L.; Menchaca, H. J. Org. Chem. 1964, 29, 2026.

esters react via cleavage of the bond between the two carbonyls.^{460,451} Similarly, 1,3-dicarbonyl compounds react with peroxyacids to give 2-hydroxy-1,3-dicarbonyls (enediols),⁴⁶¹ but 2,2-disubstituted-1,3-dicarbonyl compounds are resistant to such oxidations.⁴⁶² Ethyl acetoacetate is an example of the first type, and it gives a glycidic ester upon treatment with a peroxyacid.^{461,462} Aldehydes are easily oxidized, and reaction with peroxyacids or hydrogen peroxide usually gives a carboxylic acid (the transformation is RCHO \rightarrow RCO₂H) with little or no rearrangement. Exceptions are electron-rich aldehydes such as functionalized benzaldehyde derivatives. In these cases, formation of the formate ester is facile and is called the **Dakin reaction**.⁴⁶³ This transformation is compatible with a variety of other functionality in the substrate. In Joullie and co-worker's synthesis of ustiloxin D,⁴⁶⁴ for example, aryl aldehyde **327** (Boc = -CO2*t*-Bu) was treated with 30% hydrogen peroxide and a diselenide to give formate ester **328** via the Dakin reaction. Hydrolysis was accomplished with KOH in aqueous methanol to give phenol **329** in a yield of 73% for both steps.



3.6.B. Enzymatic Baeyer-Villiger Oxidation

Enzymatic conversion of ketones to esters is very common in microbial degradations.⁴⁶⁵ Several monooxygenases are now available for this reaction, and a correlation of enantioselectivity with a variety of substrates has been published.⁴⁶⁶ A typical transformation that can be synthetically important is the enzymatic Baeyer-Villiger oxidation reported by Walsh, which gave lactone **330** from cyclohexanone⁴⁶⁷ using a purified cyclohexanone oxygenase enzyme.⁴⁶⁸ Walsh and co-workers studied the mechanism of this reaction, and also showed that this enzyme converted

^{460.} Karrer, P.; Haab, F. Helv. Chim. Acta 1949, 32, 950.

^{461. (}a) Reference 254, p 243; (b) Karrer, P.; Kebrle, J.; Thakkar, R.M. Helv. Chim. Acta 1950, 33, 1711.

^{462.} Hassall, C.H. Org. React. 1957, 9, 73.

^{463. (}a) Dakin, H.D. Am. Chem. J. 1909, 42, 477; (b) Lee, J.D.; Uff, B.C. Quart. Rev. 1967, 21, 429 (see p 454);
(c) Dakin, H.D. Org. Synth. Coll. Vol. 1 1941, 149; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-21.

^{464.} Cao, B.; Park, H.; Joullie, M.M. J. Am. Chem. Soc. 2002, 124, 520.

^{465. (}a) Sih, C.J.; Rosazza, J.P. in Applications of Biochemical Systems in Organic Chemistry, Jones, J.B.; Sih, C.J.; Perlman, D. (Eds.), Wiley, New York, 1976, pII, pp 100-102; (b) Fonken, G.S.; Johnson, R.A. Chemical Oxidations with Microorganisms, Marcel-Dekker, New York, 1972, pp 157-164; (c) Britton, L.N.; Brand, J.M.; Markovetz, A.J. Biochim Biophys. Acta 1974, 369, 45; (d) Cripps, R.E. Biochem. J., 1975, 152, 233.

^{466.} Kyte, B.G.; Rouvière, P.; Cheng, Q.; Stewart, J.D. J. Org. Chem. 2004, 69, 12.

^{467.} Ryerson, C.C.; Ballou, D.P.; Walsh, C. Biochemistry 1982, 21, 2644.

^{468.} Donoghue, N.A.; Norris, D.B.; Trudgill, P.W. Eur. J. Biochem. 1976, 63, 175.

phenylacetaldehyde to phenylacetic acid (65% yield) accompanied by only a 12% yield of benzyl formate (PhCH₂OCHO).⁴⁶⁹ The rearrangement induced by this enzyme proceeds with completely stereochemical retention as shown by Schwab,⁴⁷⁰ analogous to the Baeyer-Villiger rearrangement that used *m*-chloroperoxybenzoic acid.



Taschner and co-workers showed that cyclohexanone oxygenase, obtained from *Acinetobacter* NCIB 9871,^{470b} converted 4-methylcyclohexanone to the corresponding γ -methyl caprolactone in 80% yield with>98% ee.^{471a} In another example, lactone **332** was prepared from bicyclic ketone **331** in 80% yield and 97% ee.^{470b} The enzymatic reaction appears to proceed in a predictable manner using the peroxide induced reaction as a model, although the enantioselectivity of the final product is influenced by the concentration of the substrate.⁴⁷² Taschner et al. found that **333** was converted to **334** in 80% yield, and in >98% ee.⁴⁷¹ This rearrangement is clearly related to similar rearrangements that use mcpba.⁴⁷³ Other enzymatic systems have been found that give a Baeyer-Villiger reaction, including the reaction of myristic acid and hydrogen peroxide catalyzed by *Candida anatarctica* lipase.⁴⁷⁴ Changing the enzymatic system can sometimes control the absolute stereochemistry of the lactone product. Oxidation of **335** with *Acinetobacter sp.* NCIB 9872 gave lactone **336**,⁴⁷⁵ but oxidation with *P. putida* NCIB 10007 gave

^{469.} Branchand, B.P.; Walsh, C.T. J. Am. Chem. Soc, 1985, 107, 2153.

^{470. (}a) Schwab, J.M. J. Am. Chem. Soc. 1981, 103, 1876; (b) Schwab, J.M.; Li, W.; Thomas, L.P. J. Am. Chem. Soc. 1983, 105, 4800.

^{471. (}a) Taschner, M.J.; Black, D.J. J. Am. Chem. Soc. 1988, 110, 6892; (b) Taschner, M.J.; Peddada, L. J. Chem. Soc. Chem. Commun. 1992, 1384; (c) Taschner, M.J.; Chen, Q.-Z., Bioorg. Med. Chem. Lett. 1991, 1, 535.

^{472.} Zambianchi, F.; Pasta, P.; Ottolina, G.; Carrea, G.; Colonna, S.; Gaggero, N.; Ward, J.M. *Tetrahedron:* Asymmetry 2000, 11, 3653.

^{473.} Ouazzani-Chahdi, J.; Buisson, D.; Azerad, R. Tetrahedron Lett. 1987, 28, 1109.

^{474.} Lemoult, S.C.; Richardson, P.F.; Roberts, S.M. J. Chem. Soc. Perkin Trans 1 1995, 89.

^{475.} Carnell, A.J.; Roberts, S.M.; Sik, V.; Willets, A.J. J. Chem. Soc. Perkin Trans. 1 1991, 2385.

lactone **337**.⁴⁷⁶ Stereochemical control is a key feature of the enzymatic Bayer-Villiger reaction.



The functional group transforms available from the Baeyer-Villiger reaction are

$$\overset{\text{RO}}{\underset{R^{1}}{\rightarrowtail}} \circ \overset{\text{O}}{\underset{R^{1}}{\searrow}} \overset{\text{O}}{\underset{R^{1}}{\longrightarrow}} \circ \overset{\text{O}}{\underset{R^{0}}{\swarrow}} \overset{\text{O}}{\underset{R^{0}}{\swarrow}} \overset{\text{O}}{\underset{R^{0}}{\swarrow}} \overset{\text{O}}{\underset{R^{0}}{\boxtimes}} \overset{\text{O}}{\underset{R^{0}}{\boxtimes} \overset{\text{O}}{\underset{R^{0}}{\boxtimes}} \overset{\text{O}}{\underset{R^{0}}{\boxtimes}} \overset{\text{O}}{\underset{R^{0}}{\boxtimes}} \overset{\text{O}}{\underset{R^{0}}{\boxtimes}} \overset{\text{O}}{\underset{R^{0}}{\boxtimes}} \overset{\text{O}}{\underset{R^{0}}{\boxtimes}} \overset{\text{O}}{\underset{R^{0}}{\varinjlim}} \overset{\text{O}}{\underset{R^{0}}{\underset{R^{0}}{\varinjlim}} \overset{\text{O}}{\underset{R^{0}}{\underset{R^{0}}{\varinjlim}} \overset{\text{O}}{\underset{R^{0}}{\underset{R^{0}}{\underset{R^{0}}{\underset}} \overset{\text{O}}{\underset{R^{0}}{\underset}} \overset{\text{O}}{\underset{R^{0}}{\underset}} \overset{\text{O}}{\underset{R^{0}}{\underset}} \overset{\text{O}}{\underset{R^{0}}{\underset{R^{0}}{\underset{R^{0}}{\underset}} \overset{\text{O}}{\underset{R^$$

3.7. OXIDATIVE BOND CLEAVAGE (C=C \rightarrow C=O + O=C)

3.7.A. Cleavage of Alkenes by Transition Metals

Alkenes can be oxidized to epoxides or 1,2-diols by various reagents.⁴⁷⁷ If more powerful oxidizing agents are used, however, the C=C moiety can be cleaved into two carbonyl derivatives. This section will discuss the various reagents that effect this transformation.

3.7.A.i. Potassium Permanganate. In Section 3.5.A, treatment of alkenes with dilute solutions of potassium permanganate was shown to give a one-stage oxidation to 1,2-diols in excellent yield. More concentrated solutions and higher temperatures lead to cleavage of the alkene to a diacid via oxidation of an intermediate diol (**338**), usually in acidic media⁴⁷⁸ The terms hot and concentrated are ambiguous and are used for concentrations that range from a >10% solution of permanganate to 10 M solutions, and temperatures that range from ambient to > 100°C. An important modification that increases the synthetic utility of the reaction mixes periodic acid (HIO₄)⁴⁷⁹ with a catalytic amount of permanganate (called the **Lemieux-von Rudloff reagent**).⁴⁸⁰ The stoichiometric oxidant HIO₄ oxidizes the manganate product back to permanganate, allowing oxidative cleavage of alkenes under catalytic conditions. A solution of potassium permanganate in benzene with the well-known potassium complexing agent dicyclohexyl-18-crown-6 is very effective for cleaving alkenes to acid products,⁴⁸¹ as illustrated

^{476.} Grogan, G.; Roberts, S.M.; Willets, A.J. J. Chem. Soc. Chem. Commun. 1993, 699. For the use of this lactone in a synthesis, see Velázquez, F.; Olivo, H.F. Org. Lett. 2000, 2, 1931.

^{477.} Reference 20, pp 1650-1652.

 ^{478. (}a) Wolfe, S.; Ingold, C.K.; Lemieux, R.U. J. Am. Chem. Soc. 1981, 103, 938; (b) Wolfe, S.; Ingold, C.K. Ibid. 1981, 103, 940.

^{479.} Smith, M.B.; March, J. March's Advanced Organic Chemistry, 6th ed., Wiley, New York, 2007, p. 1743.

^{480. (}a) Lemieux, R.U.; von Rudloff, E. *Can. J. Chem.* **1955**, *33*, 1701, 1710; (b) von Rudloff, E. *Ibid.* **1955**, *33*, 1714; (c) von Rudloff, E. *Ibid.* **1956**, *34*, 1413; (d) von Rudloff, E. *Ibid.* **1965**, *43*, 1784.

^{481. (}a) Sam, D.J.; Simmons, H.E. J. Am. Chem. Soc. 1972, 94, 4024; (b) Lee, D.G.; Chang, V.S. J. Org. Chem. 1978, 43, 1532.

by the cleavage of cyclohexene to adipic acid.



Oxidation of disubstituted alkenes bearing one or more C=C-H units leads to aldehydes, but the aldehyde is further oxidized to a carboxylic acid. Although isolation of the aldehyde can be difficult, it is possible. An example is the oxidation of bicyclo[3.3.1]hept-2-ene (norbornene, **339**) with aqueous permanganate and magnesium sulfate, which gave dialdehyde **340** in up to 66% yield.⁴⁸² It is also possible to obtain aromatic aldehydes from aryl substituted alkenes by permanganate oxidation in aqueous media, but good yields are obtained only when the aromatic ring has ortho- or para-electron withdrawing substituents.^{483,484} The presence of conjugating groups on the alkene increases the rate of oxidation, but bulky groups on the alkene greatly reduce the yield of aldehyde products. It is also possible to oxidize alkynes with permanganate. Midland showed that **341** was oxidized to 2-acetoxyheptanoic acid (**342**) in 92% yield using an excess of permanganate in acetic acid.⁴⁸⁵



Potassium permanganate is a very powerful reagent and can oxidize alkyl fragments (sec. 3.8) as well as alkenes. Straight-chain alkyl groups attached to aromatic rings are oxidized with concentrated permanganate to give benzoic acid derivatives, as in the oxidation of 2-chlorotoluene to 2-chlorobenzoic acid.⁴⁸⁶ Similarly, 2-methylpyridine was oxidized to pyridine 2-carboxylic acid.⁴⁸⁷

3.7.A.ii. Osmium Reagents. When alkenes are oxidized with a mixture of OsO_4 and $NaIO_4$ (the Lemieux-Johnson reagent),⁴⁸⁸ oxidative cleavage leads to aldehydes and ketone products. This

^{482. (}a) Reference 233a, p 125; (b) Wiberg, K.B.; Saegebarth, K.A. J. Am. Chem. Soc. 1957, 79, 2822.

^{483.} Reference 233a, pp 124.

^{484.} Viski, P.; Szeverényi, Z.; Simándi, L. J. Org. Chem. 1986, 51, 3213.

^{485. (}a) Midland, M.M.; Lee, P.E. J. Org. Chem. 1981, 46, 3933; (b) Krapcho, A.P.; Larson, J.R.; Eldridge, J.M. Ibid. 1977, 42, 3749.

^{486.} Clarke, H.T.; Taylor, E.R. Org. Synth. Coll. Vol. 2 1943, 135.

^{487.} Singer, A.W.; McElvain, S.M. Org. Synth. Coll. Vol. 3 1955, 740.

^{488. (}a) Reference 233a, p 122; (b) Pappo, R.; Allen, Jr., D.S.; Lemieux, R.U.; Johnson, W.S. J. Org. Chem. 1956, 21, 478.

technique requires only 1-5 mol% of osmium tetroxide, which is important given the expense and toxicity of osmium compounds. Nemoto and co-workers used this reagent to cleave the vinyl unit in **343** to the aldehyde moiety in **344** as part of the synthesis of macrosphelide A.⁴⁸⁹ *N*-Methylmorpholine *N*-oxide is sometimes added to the reaction. Paquette et al. used this variation in a synthesis of (–)-polycavernoside A.⁴⁹⁰



3.7.A.iii. Ruthenium Reagents. Ruthenium compounds are powerful oxidizing agents that are capable of cleaving alkenes. Ruthenium tetroxide (RuO_4) showed a reduction potential of 0.59 V in the following reaction:¹⁷

$$RuO_4 + e^- \rightarrow RuO_4^{2-} \qquad \qquad 0.59 V$$

Ruthenium tetroxide cleaves alkenes to give ketones, aldehydes, or carboxylic acids.⁴⁹¹ Halogenated solvents such as dichloromethane are commonly used, since ether, benzene and pyridine <u>react violently</u> with ruthenium tetroxide.⁴⁹² The yield of cleavage products is variable and sometimes low (cyclohexene, for example, gave adipaldehyde in only 10% yield).^{493,491} Yields of the oxidative cleavage products were greatly improved by addition of sodium periodate (NaIO₄) to the reaction.⁴⁹⁴ A disadvantage of the RuO₄/NaIO₄ reagent is that alkenyl carbons bearing a hydrogen atom are usually oxidized to the acid rather than the aldehyde.⁴⁹⁵ Other ruthenium salts also give excellent yields of cleavage products, particularly when mixed with sodium periodate. In its initial formulation, Sharpless used RuO₂ and NaIO₄ for the oxidation but he also showed that ruthenium trichloride (RuCl₃) and sodium periodate give selective oxidative cleavage to the acid in good yield.⁴⁹⁶ It is relatively easy to oxidize tetrasubstituted alkenes, as in Mehta's synthesis of precapnelladiene using a mixture of RuO₂ and NaIO₄ to oxidize a bicyclic alkene to a cyclooctadione derivative.⁴⁹⁷ This reagent is useful for more complex targets. In a semisynthesis of heterocyclic analogs of squamocin, for example, Lewin

- 491. Reference 233a, p 128.
- 492. Berkowitz, L.M.; Rylander, P.N. J. Am. Chem. Soc. 1958, 80, 6682.
- 493. (a) Djerassi, C.; Engle, R.R. J. Am. Chem. Soc. 1953, 75, 3838; (b) see also, Munavalli, S.; Ourisson, G. Bull. Chim. Soc. Fr. 1964, 729 for use in a synthesis of longifolene.
- 494. (a) Reference 224a, p 129; (b) Pappo, R.; Becker, A. Bull. Res. Counc. Isr. Sect. A 1956, 5A, 300; (c) Sarel, S.; Yanuka, Y. J. Org. Chem. 1959, 24, 2018.
- 495. Stork, G.; Meisels, A.; Davies, J.E. J. Am. Chem. Soc. 1963, 85, 3419.
- 496. Carlsen, P.H.J.; Katsuki, T.; Martin, V.S.; Sharpless, K.B. J. Org. Chem. 1981, 46, 3936.
- 497. Mehta, G.; Murthy, A.N. J. Org. Chem. 1987, 52, 2875.

^{489.} Kawaguchi, T.; Funamori, N.; Matsuya, Y.; Nemoto, H. J. Org. Chem. 2004, 69, 505.

^{490.} Paquette, L.A.; Barriault, L.; Pissarnitski, D. J. Am. Chem. Soc. 1999, 121, 4542.

and co-workers treated $OSiMe_2t$ -Bu-protected (sec. 7.3.A.1) squamocin (**345**) with RuCl₃ and NaIO₄, and obtained keto-ester **346** in 86% yield.⁴⁹⁸



A key ingredient in the RuCl₃/NaIO₄ oxidation appears to be the choice of solvent, and acetonitrile is frequently used. Alkenes containing a C=C–H unit, such as 1-nonene, are cleaved to acids (nonanoic acid, 89% yield).⁴⁹⁶ Alcohols (see **347**) can be oxidized to the acid (in this case, **348** was formed without disturbing the adjacent epoxide) and 1,2-diols are cleaved to the acid in high yield.⁴⁹⁶ The oxidations are not accompanied by racemization or rearrangement, which is important when the site of oxidation is adjacent to a stereogenic center (see **345** or **347**).⁴⁹⁶ In some cases, secondary reactions can accompany the oxidation. In Silverstein's synthesis of optically pure grandisol,⁴⁹⁹ **349** was opened to the diacid (**350**) and ketone **351** was formed after oxidative decarboxylation under the reaction conditions.



3.7.A.iv. Chromium Reagents. It is clear from previous discussions in this chapter that Cr(VI) is a powerful oxidant. Indeed, Cr(VI) can cleave alkenes to the corresponding carbonyl compound. It is often difficult to limit the extent of oxidation, however, and the products include "epoxides, ketols, and acids and ketones arising from cleavage or rearrangement reactions".⁵⁰⁰ Chromium

^{498.} Duval, R.; Lewin, G.; Hocquemiller, R. Bioorg. Med., Chem. 2003, 11, 3439.

^{499.} Webster, F.X.; Silverstein, R.M. J. Org. Chem. 1986, 51, 5226.

^{500.} Reference 233a, p 148.

oxidation of 1,1-diphenylalkenes, however, is the basis of the classical **Barbier-Wieland degradation**, which removes one carbon from the starting molecule.⁵⁰¹ Wieland used this method for the conversion of desoxycholic acid (**352**) to nordesoxycholic acid (**353**), in which two carbons are cleaved (one at a time) from the carboxylic acid chain by sequential Barbier-Wieland degradations.⁵⁰² The first sequence with **352** (esterification, reaction with phenylmagnesium bromide and then oxidative cleavage) gave **353**, and the second sequence gave **359**.



The **Gallagher-Hollander degradation**⁵⁰³ is a related oxidative cleavage sequence that removes two carbons from the original molecule. The original acid is converted to a diazoketone (see sec. 13.9.B.iii for other applications of diazoketones) and hydrolysis generates a methyl ketone. Bromination of the methyl ketone is followed by elimination (induced by collidine), which generates a conjugated ketone. Oxidative cleavage with chromium trioxide completes the sequence, giving a new acid with a net loss of two carbons.⁵⁰³ A modification of the Barbier-Wieland degradation allows removal of three carbons and is called the **Miescher degradation**.⁵⁰⁴ Initial reaction converts the acid to an ester and reaction with phenylmagnesium bromide generates the diphenylalkylidene intermediate that was important to the Barbier-Wieland sequence. Subsequent treatment with NBS (sec. 2.8.B) gives an allylic bromide, and elimination with methanolic potassium carbonate (K₂CO₃) leads to a conjugated diene. Oxidative cleavage with chromium trioxide cleaves three carbons from the original molecule. These techniques shorten a long chain carboxylic acid by one, two or three carbons in a convenient manner.

The functional group transforms for oxidative cleavage with metals are



^{501. (}a) Wieland, H. Berichte 1912, 45, 484; (b) Barbier, P.; Locquin, R. Compt. Rend. 1913, 156, 1443; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-5.

- 502. Riegel, B.; Moffatt, R.B.; McIntosh, A.V. Org. Synth. Coll. Vol. 3 1955, 237, 234.
- 503. Hollander, V.P.; Gallagher, T.F. J. Biol. Chem. 1946, 162, 549.

^{504. (}a) Meystre, C.; Frey, H.; Wettstein, A.; Miescher, K. *Helv. Chim. Acta* 1944, 27, 1815; (b) Rodd, E.H. *Chemistry of Carbon Compounds*, 2, 1962, pp 117, 796, 903; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-61.

3.7.B. Cleavage of Alkenes with Ozone

Ozone (O_3) is a powerful oxidizing agent. The reduction potential is high in both acidic and basic media, is 2.07 and 1.24 V, respectively for the following reactions.¹⁷

$$O_3 + 2 H^+ + 2 e^- \rightarrow O_2 + H_2O$$
 2.07 V

$$O_3 + H_2O + 2e^- \rightarrow O_2 + 2HO^-$$
 1.24 V

Ozone occurs naturally in the atmosphere but in too low a concentration for convenient use. In the laboratory, ozone is produced by electric discharge in oxygen. Ozone is a resonance stabilized species with four contributors, but contributors **355A** and **355B** are most useful⁵⁰⁵ for

$$-0^{+}$$
 0^{+} 0^{+} 0^{+} 0^{-} 0^{-} 0^{-} 0^{+} $0^{$

understanding reactions with alkenes. Alkenes react via a 1,3-dipolar addition⁵⁰⁶ mechanism (discussed in sec. 11.11.A) to give a 1,2,3-trioxolane product (**356**). This trioxolane is thermally unstable, even at low temperatures, and rapidly rearranges to a 1,2,4-trioxolane, better known as an ozonide (**359**).^{505,506} The accepted mechanism of this rearrangement was proposed by Criegee,^{507b} in which cleavage of an O-O bond in trioxolane **356** gives a ketone (or aldehyde) and a carbonyl oxide (**357**). These two products do not drift apart, however, but react as shown to give the ozonide, **359**. Other reaction pathways are possible with the carbonyl oxide. When the carbonyl partner is an aldehyde, ozonide formation is preferred in virtually all cases. When the partner is a ketone, another pathway is sometimes seen, in which **357** dimerizes to a tetraoxone (**358**) or polymerizes to a polyperoxide.⁵⁰⁸ Criegee showed that alkoxyhydroperoxides (**360**) were formed when methanol was used as a solvent, and carboalkoxyhydroperoxides (**361**) was observed when acetic acid was used as a solvent.⁵⁰⁹



^{505. (}a) Belew, J.S. Oxidation, Vol. 1, Augustine, R.L. (Ed.), Marcel Dekker, New York, 1969, p 262; (b) Meinwald, J. Chem. Ber. 1955, 88, 1889; (c) Wibaut, J.P.; Sixma, F.L.J.; Kampschmidt, L.W.F.; Boer, H. Rec. Trav. Chim. 1950, 69, 1355.

- 507. (a) Reference 505a, p 263 and reference 7 therein; (b) Creigee, R. Record Chem. Progr. 1957, 18, 111.
- 508. (a) Reference 505a, pp 262-267; (b) Reference 233a, p 120.

^{506.} Criegee, R. Angew. Chem. Int. Ed. 1975, 14, 745.

^{509.} Reference 505a, p 265.



Several studies have examined cis/trans isomerism in the ozonide⁵¹⁰ but this section will focus only on products derived *from* the ozonide (aldehydes, ketones, and acids). The geometry of the alkyl groups on the ozonide will not be discussed except to say that cis-alkenes give both cis- and trans-ozonides, with the cis generally predominating. Similarly, trans-alkenes give higher yields of the trans-ozonide. In many cases, however, the cis/trans ratio is close to 1:1.⁵¹¹ In general, electron rich alkenes are oxidized faster than electron-poor alkenes.

An ozonide such as **362** can be decomposed by four methods: (1) reduction, (2) hydrolysis, (3) oxidation, or (4) thermolysis.⁵¹² If the ozonide carbons bear a hydrogen (CHR³ in **362**), reductive decomposition usually gives the corresponding aldehyde whereas an acidic or oxidative workup will yield the acid (by oxidation of the aldehyde in most cases).⁵¹³ When that carbon bears two carbon groups (CR¹R₂ in **362**), the product is a ketone by either oxidative or reductive methods. It is likely that reduction of the peroxide linkage in **362** first yields a bridged hemiacetal (**363**),⁵¹⁴ which fragments to the carbonyl derivatives with loss of water. Hydrolysis of the ozonide apparently occurs at a O-C-O linkage and the peroxide linkage (C-O-O-C) to give the peroxy hemiacetal (structurally related to **360** but with an OH rather than OMe).⁵¹⁴

$$\overset{R^{1}}{\underset{R^{2}}{\rightarrowtail}} O + O = \overset{R^{3}}{\underset{OH}{\leftarrow}} \overset{\text{oxidation}}{\underset{R^{2}}{\longleftarrow}} \overset{R^{1}}{\underset{O-O}{\longleftarrow}} \overset{R^{3}}{\underset{H}{\longrightarrow}} \overset{\text{reduction}}{\underset{OH}{\leftarrow}} \left[\overset{R^{1}}{\underset{OH}{\leftarrow}} \overset{R^{3}}{\underset{OH}{\longleftarrow}} \underset{OH}{\underset{OH}{\leftarrow}} \overset{R^{1}}{\underset{H}{\longrightarrow}} \overset{R^{1}}{\underset{R^{2}}{\longleftarrow}} O + O = \overset{R^{3}}{\underset{H}{\leftarrow}} \overset{R^{3}}{\underset{H}{\longrightarrow}} \overset{R^{1}}{\underset{H}{\longrightarrow}} O + O = \overset{R^{3}}{\underset{H}{\leftarrow}} \overset{R^{3}}{\underset{H}{\longrightarrow}} \overset{R^{1}}{\underset{H}{\longrightarrow}} O + O = \overset{R^{3}}{\underset{H}{\leftarrow}} \overset{R^{3}}{\underset{H}{\longrightarrow}} O + O = \overset{R^{3}}{\underset{H}{\longrightarrow}}$$

Reduction of the ozonide with lithium aluminum hydride (sec. 4.2.C.ii) or sodium borohydride (sec. 4.4.A) generates alcohol products⁵¹⁵ as expected, by further reducing the initially formed carbonyl products. Note that one equivalent of LiAlH₄ is required per equivalent of ozonide, and the temperature is typically below -10° C.⁵¹⁶ To prevent over-reduction, the most common reagents that decompose an ozonide to produce aldehyde and ketone products are zinc/acetic acid, dimethyl sulfide (DMS) or triphenylphosphine.

A typical example using ozonolysis in synthesis is the cleavage of the alkene unit in 364 to

513. Reference 20, pp 1632-1633.

^{510.} Reference 505a, pp 267-272 and references cited therein.

^{511. (}a) Reference 505a, p 268; (b) Murray, R.W.; Youssefyeh, R.D.; Story, P.R. J. Am. Chem. Soc. 1967, 89, 2429.

^{512.} Reference 505a, p 298.

^{514.} Reference 505a, p 299.

^{515. (}a) Reference 233a, p 121; (b) Reference 505a, p 299.

^{516. (}a) Reference 505a, p 301; (b) Greenwood, F.L. J. Org. Chem. 1955, 20, 803.

give aldehyde **365** with loss of formaldehyde, taken from Fukuyama and co-worker's synthesis of (–)-kainic acid.⁵¹⁷ Ozonolysis of bicyclic alkenes can be used to generate relative large, difunctionalized compound. In a synthesis of deacetoxyalcyonin acetate,⁵¹⁸ Molander and co-workers subjected **366** to ozonolysis and a reductive workup with dimethyl sulfide gave diketone **367**.



It is possible to trap an aldehyde product of ozonolysis as an acetal using what is called the **Schreiber protocol.**⁵¹⁹ In Fürstner's synthesis of (*R*)-(+)-lasiodiplodin, cycloheptene was ozonized in the presence of methanol at -78° C,⁵²⁰ which was followed by neutralization with bicarbonate and dimethyl sulfide to give aldehyde-acetal **368**. This method is quite useful for the chemical differentiation of the two aldehyde units that result from simple ozonolysis of the cyclic alkene.

$$(1. O_3, MeOH, CH_2Cl_2) \xrightarrow{OMe}_{MeO} (CHO)$$

An oxidative workup with ozonides such as **362** uses reagents such as hydrogen peroxide, peroxy acids, silver oxide, chromic acid or permanganate, and produces acids. The conversion of cyclohexene to adipic acid by treatment with (1) O_3 and (2) H_2O_2 is a simple example.⁵²¹ As noted above, when the ozonide is disubstituted (two carbon groups on the initial carbon of the alkene), the product is a ketone and either oxidative and reductive workups can be used. If that carbon bears an hydrogen, the oxidative workup will produce an acid and a reductive workup of the aldehyde, as discussed above.

Sterically hindered alkenes react with ozone approximately as fast as unsubstituted alkenes. Ozonolysis of 2,2,5,5-tetramethyl-3-(1,1-dimethylethyl)-3-hexene, for example, gave

^{517.} Torihata, M.; Nakahata, T.; Kuwahara, S. Org. Lett. 2007, 9, 2557.

^{518.} Molander, G.A.; St. Jean Jr., D.J.; Haas, J. J. Am. Chem. Soc. 2004, 126, 1642.

^{519.} Schreiber, S.L.; Clause, R.E.; Reagan, J. Tetrahedron Lett. 1982, 23, 3867.

^{520.} Fürstner, A.; Thiel, O.R.; Kindler, N.; Bartkowska, B. J. Org. Chem. 2000, 65, 7990.

^{521.} Bailey, P.S. J. Org. Chem. 1957, 22, 1548.

pivalaldehyde and di-*tert*-butyl ketone using trimethyl phosphite as a reducing agent.⁵²² Steric hindrance is a factor in some cases, however, as in the ozonolysis of **369**, which gave an epoxide (**370**) in 70% yield rather than oxidative cleavage.^{523a} This is what Bailey and Lane called partial cleavage, and it is sometimes observed with highly hindered alkenes.^{523b} The product distribution depends upon the solvent that is used.^{523,524,525}



An ozonide can rearrange prior to cleavage if a reactive functional group is adjacent to the carbon bearing the ozonide oxygen. Cargill and Wright used this abnormal reaction in a synthesis of grandisol,⁵²⁶ where ozonolysis of **371** initially formed the expected ozonide (**372**). Fragmentation of **371**, initiated by the adjacent hydroxyl group, gave keto acid **373** as shown.



Some aromatic compounds can also react with ozone, although most simple aromatic rings such as benzene derivatives and naphthalene do not. Anthracene reacted with ozone to give anthraquinone in 73% yield after an oxidative workup.⁵²⁷ Indeed, quinone formation is a more typical example of the reaction of ozone with aromatic compounds (for other oxidative cleavage reactions see sec. 3.8 and for oxidation to phenols and quinones see sec. 3.3). Only a reactive π bond, such as the 9,10 bond of phenanthrene, will oxidatively cleave. Oxidation of phenanthrene (**374**) gave dialdehyde **375** upon treatment with ozone in methanol followed by a workup with potassium iodide in acetic acid.⁵²⁸

^{522.} Abruscato, G.J.; Tidwell, T.T. J. Org. Chem. 1972, 37, 4151.

^{523. (}a)Hochstetler, A.R. J. Org. Chem. 1975, 40, 1536; (b)Bailey, P.S.; Lane, A.G. J. Am. Chem. Soc. 1967, 89, 4473.

^{524.} Fuson, R.C.; Armstrong, M.D.; Wallace, W.E.; Kneisley, J.W. J. Am. Chem. Soc. 1944, 66, 1274.

^{525. (}a) Criegee, R. Product of Ozonization of Some Olefins, Advances in Chemistry Series, No. 21, American Chem. Soc. Washington, D.C.; 1959, p 133. See reference 523 and citation 3 therein; (b) Bailey, P.S.; Ward, J.W.; Hornish, R.E. J. Am. Chem. Soc. 1971, 93, 3552.

^{526.} Cargill, R.L.; Wright, B.W. J. Org. Chem. 1975, 40, 120.

^{527.} Bailey, P.S.; Kolsaker, P.; Sinha, B.; Ashton, J.B.; Dobinson, F.; Batterbee, J.E. J. Org. Chem. 1964, 29, 1400.

^{528. (}a) Reference 433a, p 358; (b) Bailey, P.S.; Erickson, R.E. Org. Synth. Coll Vol. 5 1973, 489.



The functional group transform for ozonolysis of alkenes and all oxidative cleavage reactions of alkenes can be summarized by

$$\bigwedge_{O}^{R} \bigcap_{R^{1}}^{O} \bigcap_{R^{1}}^{O} \bigcap_{R^{1}}^{C} \bigcap_{R^{1}}^{R^{1}} \bigcap_{R}^{R} \qquad \qquad \bigwedge_{O}^{R} \bigcap_{R^{1}}^{O} \bigcap_{R^{1}}^{O} \bigcap_{R^{1}}^{O} \bigcap_{R^{1}}^{R} \bigcap_{R}^{R^{1}} \bigcap_{R}^{R} \bigcap_{R}^{R^{1}} \bigcap_{R}^{R} \bigcap_{R}^$$

3.7.C. Cleavage of 1,2-Diols

Sections 3.7.A and 3.7.B showed that alkenes are oxidatively cleaved by transition metal oxidants. With certain reagents, 1,2-diols can also be oxidatively cleaved to aldehydes or ketones.⁵²⁹

3.7.C.i. Lead Tetraacetate. The reduction potentials for lead compounds were not included in Table 3.1, but lead tetraacetate [Pb(OAc)₄, LTA] is a common reagent for oxidizing organic compounds. The reduction potential for LTA in perchloric acid has been reported to be 1.6 V,⁵³⁰ making it one of the more powerful oxidants examined in this chapter. LTA is used in solvents such as acetic acid or benzene primarily for the oxidative cleavage of 1,2-diols, α -hydroxy ketones, 1,2-diketones or α -hydroxy acids.⁵³¹ Cleavage of diols probably proceeds via a cyclic intermediate such as **377**, as observed in the conversion of **376** to **378**.⁵³² The diol displaces the acetate ligands, allowing fragmentation to formaldehyde, **378** and lead (II) acetate, Pb(OAc)₂. Formation of complex **377** is structurally similar to complexes that were observed in reactions of alkenes with permanganate and osmium tetroxide (sec. 3.5). syn-Diols are oxidized faster than *anti*-diols, because cyclic intermediates **377** are formed faster with the former.⁵³³



Similar results are observed in the oxidative cleavage of diols with periodic acid. A synthetic application is the oxidative cleavage of the diol in **379** to give formaldehyde and aldehyde

^{529.} Reference 20, p 1650.

^{530.} Criegee, R. in Oxidation in Organic Chemistry, Part A, Wiberg, K.B. (Ed.), Academic Press, 1965, p 281.

^{531.} Reference 433a, pp 359-387.

^{532. (}a) Reference 433a, p 360; (b) Speer, R.J.; Mahler, H.R. J. Am. Chem. Soc. 1949, 71, 1133.

^{533.} Reference 433a, p 361.

380, taken from Trost and Brennan's synthesis of horsfiline.⁵³⁴ Unfunctionalized alkenes are unaffected by the reagent.⁵³⁵ α -Hydroxy ketones are cleaved with LTA, as in the oxidation of ketol **381** to give **382** taken from Henrick and Anderson's synthesis of gossyplure.⁵³⁶ Note that the alkene was not oxidized by LTA.



Functionalized alkenes are oxidized with LTA and a variety of interesting transformations are possible.⁵³⁷ Ethyl vinyl ether, a typical vinyl ether, gave a diacetate (2-ethoxy-1,2-ethanediol diacetate) upon treatment with LTA in acetic acid.⁵³⁸ Vinyl esters can also give α -acetoxy



ketones.⁵³⁹ Oxidation of silyl enol ethers leads to α -acetoxy ketones, illustrated by the conversion of **383** to **384** in good yield.⁵⁴⁰ Ketones and aldehydes exist in an enol form in part, and this

enol may be oxidatively cleaved with LTA to give an α -acetoxy ketone.⁵⁴¹ The yields of the α -acetoxylation product derived from methyl ketones can be improved by the addition of boron trifluoride, which acts as a catalyst.⁵⁴² Unsymmetrical dialkyl ketones react selectively at the less substituted position, presumably via the kinetic enol (sec. 9.1, 9.2.E). Oxidation of 2-butanone, for example, gave exclusively 1-acetoxy-2-butanone.⁵⁴³ Note that oxidation of α -epoxy alcohols give α -acetoxy ketones,⁵⁴⁴ and enamines undergo cleavage by LTA to form an α -acetoxy ketone but the yields are often low.⁵⁴⁵

535. For a synthetic example, see Cernigliaro, G.J.; Kocienski, P.J. J. Org. Chem. 1977, 42, 3622.

537. Butler, R.N. in Synthetic Reagents Vol. 3, Pizey, J.S. (Ed.), Ellis Horwood Ltd., Chichester, 1977, p 277-419.

539. Johnson, W.S.; Gastambide, B.; Pappo, R. J. Am. Chem. Soc. 1957, 79, 1991.

- 542. Henbest, H.B.; Jones, D.N.; Slater, G.P. J. Chem. Soc. 1961, 4472.
- 543. Moon, S.; Bohm, H. J. Org. Chem. 1972, 37, 4338.
- 544. Brocksom, T.J.; Ferreira, J.T.B.; Braga, A.L. J. Chem. Res. Synop. 1981, 334 [Chem. Abstr. 96: 85342t, 1982].

^{534.} Trost, B.M.; Brennan, M.K. Org. Lett. 2006, 8, 2027.

^{536.} Anderson, R.J.; Henrick, C.A. J. Am. Chem. Soc. 1975, 97, 4327.

^{538. (}a) Criegee, R.; Dimroth, P.; Noll, K.; Simon, R.; Weis, C. Chem. Ber. 1957, 90, 1070; (b) Levas, M. Ann. Chim. Paris 1952, 7, 697 [Chem. Abstr. 48: 1243a, 1954].

^{540.} Rubottom, J.M.; Gruber, J.M.; Kincaid, K. *Synth. Commun.* **1976**, *6*, 59; (b) Rubottom, G.M.; Marrero, R.; Gruber, J.M. *Tetrahedron* **1983**, *39*, 861.

^{541. (}a) Ichikawaki, K.; Yamaguchi, Y. J. Chem. Soc. Jpn. 1952, 73, 415; (b) Fuson, R.C.; Maynert, E.W.; Tau, T.-L.; Trumbell, E.R.; Wassmundt, F.W. J. Am. Chem. Soc. 1957, 79, 1938.

^{545. (}a) Corbani, F.; Rindone, B.; Scolastico, C. *Tetrahedron Lett.* **1972**, 2597; (b) Corbani, F.; Rindone, B.; Scolastico, C. *Tetrahedron* **1973**, *29*, 3253 and references cited therein.

3.7.C.ii. Sodium Periodate. In section 3.7.A.ii, a mixture of osmium tetroxide and periodic acid oxidatively cleaved alkenes. Sodium periodate can cleave diols directly, as in the Carreira and Lercher synthesis of strychnofoline,⁵⁴⁶ were treatment of **385** with NaIO₄ gave aldehyde **386** in >90% yield. Sodium periodate in dichloromethane, in the presence of sodium bicarbonate, has also been used.⁵⁴⁷



The disconnections for this section are



3.8. OXIDATION OF ALKYL OR ALKENYL FRAGMENTS (CH \rightarrow C=O OR C-OH)

When relatively powerful oxidizing agents are employed with *alkane* fragments that are activated by the presence of a π bond (allylic, benzylic, α -carbonyl compounds), that fragment can be oxidized to an alcohol, aldehyde or ketone, or it can be oxidatively cleaved.⁵⁴⁸ The most common reagents for these transformations are selenium dioxide (SeO₂), chromium trioxide (CrO₃), chromyl chloride (CrO₂Cl₂) or LTA. Oxidation with ruthenium compounds has been reported. Cleavage of silanes of the type R-SiMe₂Ph can be included in this section, using methodology that converts the silyl unit to an alcohol (R–OH). It has also been shown that *t*-BuOOH and CuI oxidizes the allylic carbon of alkenes to conjugated ketones.⁵⁴⁹

3.8.A Selenium Dioxide

Selenium dioxide is a common reagent used to selectively oxidize an alkyl fragment, and it is effective for converting allylic or benzylic C–H fragments to the corresponding allylic

^{546.} Lercher, A.; Carreira, E.M. J. Am. Chem. Soc. 2002, 124, 14826.

^{547.} For an example, see Alcaide, B.; Almendros, P.; Salgado, N.R. J. Org. Chem. 2000, 65, 3310.

^{548.} For oxidations of this type, see Reference 20, pp 975-976.

^{549. (}a) Salvador, J.A.R.; e Melo, M.L.Sa.; Campos Neves, A.S. *Tetrahedron Lett.* **1997**, *38*, 119. For an example taken from the synthesis of nudenoic acid, see (b) Ho, T.-L.; Su, C.-Y. J. Org. Chem. **2000**, *65*, 3566.

alcohol.⁵⁵⁰ In most applications, carbonyl derivatives are oxidized to 1,2-dicarbonyl compounds and allylic hydrocarbons to alcohols or esters.⁵⁵¹

The reaction of SeO_2 and allylic molecules proceeds via an initial **ene reaction** (see the arrows in the example and sec. 11.13) to give **387**. A 2,3-sigmatropic shift (see the arrows in the example and sec. 11.12.A) affords **388**, which is hydrolyzed to allylic alcohol **389**.⁵⁵²



It is important to note that the reaction shows an overall transformation that appears to be a direct conversion of C–H to C–OH, but in fact, the reaction is accompanied by two migrations of the π bond, as shown. Synthetic applications include oxidation of allylic positions to allylic alcohols, as in Danishefsky and co-worker's synthesis of steroid NGA0187,⁵⁵³ where **390** was converted to **391**. Notice the high selectivity of this reaction for oxidation at the less substituted carbon and in preference to the allylic methyl group side chain, for the diastereomer shown. In the presence of acetic anhydride, selenium dioxide oxidations convert the resulting allylic alcohol product to the corresponding acetate.⁵⁵⁴



Guillemonat assembled a set of rules that predict the oxidation products for different alkenes.⁵⁵⁵ Trachtenberg⁵⁵⁶ expanded the discussion of these rules to include general statements concerning oxidation with selenium dioxide and these are listed below.

555. (a) Guillemonat, A. Ann. Chim. (Paris) 1939, 11, 143; (b) Reference 552, p 267.

^{550. (}a) Trachtenberg, E.N. in *Oxidation*, Vol. 1, Augustine, R.L. (Ed.); Marcel-Dekker, New York, *1969*, pp 119-187; (b) Waitkins, G.R.; Clark, C.W. *Chem. Rev. 1945*, *36*, 235; (c) Reference 233a, p 25.

^{551.} Rabjohn, N. Org. React. 1976, 24, pp 261-426.

^{552.} Reference 233a, p 25

^{553.} Hua, Z.; Carcache, D.A.; Tian, Y.; Li, Y.-M.; Danishefsky, S.J. J. Org. Chem. 2005, 70, 9849.

^{554.} Campbell, W.P.; Harris, G.C. J. Am. Chem. Soc. 1941, 63, 2721.

^{556.} Reference 550a, pp 130-136.

- 1. Oxidation always occurs on the disubstituted side of a double bond if there is a nonbridged alkenyl hydrogen available there.
- 2. Oxidation of 1-alkylcyclohexenes occurs in the ring rather than in the side chain.
- **3.** Oxidation never occurs at bridgehead positions in bicyclic systems falling within the limits of **Bredt's rule** (sec. 6.3.B).
- 4. All other things being equal relative to the above rules, the preferred order of reactivity is $CH_2 > CH_3 > CH$.
- **5.** If the preferred allylic position is tertiary, a diene will generally be produced in preference to a tertiary alcohol.
- 6. Allylic rearrangement products can and will be formed.
- 7. Skeletal rearrangement can occur if the preferred allylic position is adjacent to a quaternary carbon or a cyclopropyl ring.

Rabjohn summarized these rules with pertinent examples.⁵⁵¹

a. In trisubstituted alkenes, oxidation occurs on the more highly substituted side of the double bond.



b. By rule (4) above, methylene is oxidized faster than CH₃ or CHR₂:



c. By rule (2) above, oxidation of cyclic alkenes usually occurs in the ring.



d. Disubstituted alkenes are oxidized in the α -position and methylene is oxidized faster than methyl or methine (rule 4) and example (b).



If the alkene is flanked by two methylene groups, both are oxidized.

e. With terminal monosubstituted alkenes the problem of allylic rearrangement is marked.

1-Butene gives a mixture of 2-buten-1-ol and 3-buten-3-ol.⁵⁵⁷ Terminal disubstituted alkenes have at least two allylic positions, as do terminal disubstituted alkenes and both are subject to oxidation. Oxidation of the unsymmetrical 4-methylcyclohexene, for example, gives different products as the reaction conditions are changed (**392-394**).



Mouseron and Jacquier showed that 392(R=H) was the major product when 4-methylcyclohexene was oxidized with selenium dioxide in acetic acid.⁵⁵⁸ When Guillemonat changed the solvent to a mixture of acetic acid and acetic anhydride, 393(R = Ac) was the major product with trace amounts of 394. The combined yield of 392-394, however, was only 19%.⁵⁵⁵ In many cases, ketone products are obtained, as in the Trost and Tang synthesis of (–)-codeine⁵⁵⁹ where 395 was converted to 396 in 58% yield.



When an electron-withdrawing group is attached to a double bond, the reaction with SeO_2 is slow relative to an unconjugated double bond. Benzylic positions react much slower than allylic positions, as seen in the conversion of the allylic site in **397** to alcohol **398**, in Mori and Tanada's synthesis of (–)-subersic acid.⁵⁶⁰



Oxidation of aldehydes and ketones to the corresponding 1,2-dicarbony is another major application of selenium dioxide.⁵⁶¹ This conversion proceeds by reaction of selenium dioxide

^{557.} Reference 550a, p 136.

^{558.} Mousseron M.; Jacquier, R. Bull. Chim. Soc. Fr. 1952, 467.

^{559.} Trost, B.M.; Tang, W. J. Am. Chem. Soc. 2002, 124, 14542.

^{560.} Tanada, Y.; Mori, K. Eur. J. Org. Chem. 2003, 848.

^{561.} Reference 550a, pp 153-174.

with the enol form of the carbonyl (**399**) to give the selenous enol ester, **400**. Oxidative rearrangement to **401** is followed by loss of selenium and water to give the dicarbonyl (here, diketone **402**).⁵⁶² Cyclohexanone was converted to cyclohexane-1,2-dione in 60% yield with $SeO_{2,}^{563}$ and similar oxidation of aldehydes led to glyoxals in good yield. Methyl ketones can be oxidized to glyoxals, as in the conversion of acetophenone to **403** in 72% yield.⁵⁶⁴ In unsymmetrical ketones oxidation occurs preferentially at the less sterically hindered position,⁵⁶⁵ which is probably related to the relative stability of the enol assumed to be the reactive intermediate in the formation of **403**. The hydrogen on the carbon β to the oxoseleno moiety can be removed in some cases, forming an aldehyde by an E2 type elimination.⁵⁶⁶ Aldehyde formation is an important reaction only when the α -hydrogen is sterically hindered⁵⁶⁷ and is especially important in reactions with ketones.⁵⁶⁸ In addition to oxidizing an allylic CH unit or positions α to a carbonyl, selenium dioxide also oxidizes benzylic positions to a carbonyl derivative, without oxidizing the aromatic ring.



The functional group transforms available from selenium dioxide oxidations are



3.8.B. Chromium Trioxide Oxidation

In addition to the many reactions of Cr(VI) noted in this chapter, it is also capable of oxidizing the C-H bond of certain hydrocarbons is also possible. In general, tertiary C-H is cleaved

^{562.} Reference 550a, p 163.

^{563. (}a) Riley, H.L.; Morley, J.F.; Friend, N.A.C. J. Chem. Soc. 1932, 1875; (b) Hach, C.C.; Banks, C.V.; Diehl, H. Org. Synth. Coll. Vol. 4 1963, 229.

^{564. (}a) Riley, H.A.; Gray, A.R. Org. Synth. Coll. Vol. 2 1943, 509; (b) Fieser, L.F.; Fieser, M. Reagents for Organic Synthesis Vol. 1; Wiley, New York, 1967, p 993.

^{565.} Reference 550a, p 158.

^{566.} Reference 550a, pp 166-174.

^{567. (}a) Reference 551, p 273; (b) Meystre, Ch.; Frey, H.; Voser, W.; Wettstein, A. *Helv. Chim. Acta* **1956**, *39*, 734; (c) Szpilfogel, S.; Posthumus, T.; DeWinter, M.; Van Dorp, D.A. *Rec. Trav. Chim.* **1956**, *75*, 475.

^{568.} Reference 551, pp 273-275.

before secondary and secondary before primary. The initial product of this oxidation is usually an alcohol, which can be eliminated to give an alkene or be further oxidized to a ketone or acid. It is also possible to oxidize ketones to acids by oxidative cleavage. In the reactions just mentioned, it is difficult to control overoxidation and this method has little synthetic value, although methyl ketones can be oxidized to the acid [R₂CH(C=O)Me \rightarrow R₂C-CO₂H], with CrO₃. Chromium oxide can also oxidize benzylic positions, as in the **Étard reaction** (see sec. 3.8.E), or allylic positions. In a synthesis of the shark repellent pavoninin-4,⁵⁶⁹ Williams and co-workers oxidized the allylic position in **404** with chromium trioxide in the presence of 3,5dimethylpyrazole to give a 62% yield of conjugated ketone **405**.



Another hydrocarbon reaction is somewhat dated, the classical **Kuhn-Roth oxidation**.⁵⁷⁰ This method allows one to determine the number of methyl groups present in a molecule. Chromium trioxide in concentrated sulfuric acid oxidatively cleaves methyl groups to acetic acid, and titration with standardized base gives to the number of equivalents of acid formed, which corresponds to the number of methyl groups in the original molecule. Kuhn-Roth oxidation of 2-methylpyridine, for example gave about one equivalent of acetic acid.^{571b} and oxidation of fatty acids or alcohols (with chain lengths up to 20 carbons)⁵⁷¹ gave one or more equivalents of acetic acid. Modification of the oxidation step allows determination of the number of methyl groups in fatty acids of > 20 carbons.⁵⁷² For fatty acids of > 20 carbon atoms, poor solubility of the organic compound led to incomplete oxidation and too few equivalents of acetic acid were observed. Prior dissolution of the acid or alcohol in sulfuric acid, followed by

addition of chromium trioxide, gave improved yields and reduced decomposition. Kirste and Stenhagen⁵⁷² showed that **406** released about two equivalents of acetic acid. Ginger⁵⁷¹ observed that 1.65 equivalents of acetic acid were formed from α -methylstearic acid (**407**), in what is probably a typical experimental result for a Kuhn-Roth oxidation.



^{569.} Williams, J.R.; Gong, H.; Hoff, N.; Olubodun, O.I. J. Org. Chem. 2005, 70, 10732.

^{570. (}a) Kühn, R.; Roth, H. Berichte, 1933, 66, 1274; (b) Franck, B.; Knoke, J. Ibid. 1962, 95, 579.

^{571.} Ginger, L.G. J. Biol. Chem. 1944, 156, 453.

^{572.} Kirsten, W.; Stenhagen, E. Acta Chem. Scand. 1952, 6, 682.

3.8.C. Oxidation with Ruthenium Compounds

Ruthenium salts in combination with peroxide, particularly alkyl hydroperoxides, oxidize methylene units to the corresponding carbonyl. The reaction is most effective for allylic methylene units and methylene units adjacent to heteroatoms. Ruthenium (III) chloride and *tert*-butyl hydroperoxide is an effective reagent for this transformation.⁵⁷³ In a synthesis of the anti-asthma agent IPL576,092, Shen and Burgoyne converted **408** to **409** in 56% yield.⁵⁷⁴ Those authors accomplished the same transformation using a mixture of chromium trioxide (see above), 3,5-dimethylpyrazole in dichloromethane at -20°C. As suggested above, the oxidation is not limited to the formation of ketones. When 3-hydroxyproline derivative **410** was treated with a mixture of ruthenium oxide and sodium periodate, lactam **411** was formed in >95% yield.⁵⁷⁵ This particular oxidation was based on earlier work of Yoshifuji and Kamane, who used this reagent for the conversion of cyclic α -amino acids to α -amino dicarboxylic acids.⁵⁷⁶ It is clear that the ruthenium-based oxidation reaction of methylene units is both versatile and general.



3.8.D. Tamao-Fleming Oxidation

Just as carbon-based alkyl groups can be oxidized, a silane unit can be oxidized under certain conditions. Alkylsilanes can be converted to a hydroxy unit, but either an aryl group⁵⁷⁷ (R–SiR'₂Ar) or another silyl group⁵⁷⁸ (RSi–SiR'₃) must be attached to silicon. In an early version of this reaction, Fleming used a two-step process to transform the silane unit to an

^{573.} Miller, R.A.; Li, W.; Humphrey, J.L. Tetrahedron Lett. 1996, 37, 3429.

^{574.} Shen, Y.; Burgyone, D.L. J. Org. Chem. 2002, 67, 3908.

^{575.} Zhang, X.; Schmitt, A.C.; Jiang, W. Tetrahedron Lett, 2001, 42, 5335.

^{576. (}a) Yoshifuji, S.; Kamane, M. *Chem. Pharm. Bull.* **1995**, *43*, 1617; (b) Kamane, M.; Yoshifuji, S. *Tetrahedron Lett.* **1992**, *33*, 8103; (c) Tanaka, K.; Sawanishi, H. *Tetrahedron: Asymmetry* **1998**, *9*, 71.

^{577. (}a) Kumada, M.; Tamao, K.; Yoshida, J.I. J. Organomet. Chem. 1982, 239, 115; (b) Tamao, K.; Kakui, T.; Akita, M.; Iwahara, T.; Kanatani, R.; Yoshida, J.; Kumada, M. Tetrahedron 1983, 39, 983; (c) Fleming, I.; Henning, R.; Plaut, H. J. Chem. Soc. Chem. Commun. 1984, 29.

^{578.} Suginome, M.; Matsunaga, S.; Ito, Y. Synlett 1995, 941.

alcohol unit. Treatment with mercuric acetate and peroxyacetic acid, followed by reduction with lithium aluminum hydride (see sec. 4.2.A for reductions with LiAlH₄) gave the alcohol. Malacria and co-workers used this approach to convert **412** to alcohol **413** in 78% yield, in a synthesis of deoxymannojirimycin.⁵⁷⁹ Note that a reduction step was not required.



There were several cases when this original procedure failed, but it was discovered that if the silane units are treated with a fluorinating agent such as TBAF or CsF, the Ar or SiR'₃ unit is replaced with F.⁵⁸⁰ Subsequent treatment with hydrogen peroxide or a peroxy acid gave the alcohol. This sequence is often called the **Tamao-Fleming oxidation**.⁵⁷⁷ In synthetic studies for (+)-pramanicin, Barrett and co-workers found the original procedure failed but the Tamao-Fleming procedure using mcpba-KHF₂ converted **414** to **415** in 70% yield.⁵⁸¹ One of the more attractive features of this oxidation is that the absolute stereochemistry of the C–Si bond in **414** is retained in the C–O bond of **415**. In other words, the reaction proceeds with retention of stereochemistry of the silyl group. Another variation uses KF and hydrogen peroxide for the oxidation, a reaction used by Overman and co-workers for one step of a synthesis of (+)-aloperine.⁵⁸²



Incorporation of the silvl unit can be done in several ways,⁵⁸³ including conjugate addition of silvlcuprates to conjugated carbonyl compounds (see sec. 8.7.A.vi.). A brief discussion of silane carbanions will be presented in section 8.10.

The functional group transforms available from selenium dioxide oxidations are

$$\begin{array}{c} R \\ \searrow \\ R \end{array} \rightarrow OH \quad \Box \searrow \quad \begin{array}{c} R \\ \longrightarrow \\ R \end{array} \rightarrow SiR_3$$

^{579.} Boglio, C.; Stahlke, S.; Thorimbert, S.; Malacria, M. Org. Lett 2005, 7, 4851.

^{580.} For the protodesilylation step see (a) Häbich, D.; Effenberger, F. *Synthesis* 1979, 841. For the peroxyacid reaction see (b) Buncel. E.; Davies, A.G. J. Chem. Soc. 1958, 1550.

^{581.} Barrett, A.G.M.; Head, J.; Smith, M.L.; Stock, N.S.; White, A.J.P.; Williams, D.J.J. Org. Chem. 1999, 64, 6005.

^{582.} Brosius, A.D.; Overman, L.E.; Schwink, L. J. Am. Chem. Soc. 1999, 121, 700.

For examples see (a) Matsumoto, Y.; Hayashi, T.; Ito, Y. *Tetrahedron* 1994, 50, 335; Uozumi, Y.; Kitayama, K.; (b) Hayashi, T.; Yanagi, K.; Fukuyo, E. *Bull. Chem. Soc. Jpn.* 1995, 68, 713.

3.8.E. Alkene Oxidation (C=C \rightarrow C-C=O)

Tansition metal derivatives can convert alkenes into a carbonyl derivative with rearrangement, but *without* bond cleavage.⁵⁸⁴ This section will briefly discuss several of these reagents and their reactions. A common one is chromyl chloride (CrO₂Cl₂), which reacts with 1,1-disubstituted terminal alkenes [R₂C=CH₂] to give the corresponding aldehyde.⁵⁸⁵ Oxidation of 1,1-diphenylethene with chromyl chloride required a reductive workup with zinc (to reduce the chromium intermediate) but gave diphenylacetaldehyde in 63% yield.⁵⁸⁶ This interesting conversion is a synthetically useful method for the preparation of α , α -disubstituted aldehydes.

The **Étard reaction** (see sec. 3.8.B)⁵⁸⁷ used this reagent for the oxidation of methylated aryl derivatives to the corresponding aryl aldehyde. Tillotson and Houston found that the Étard reaction is catalyzed by small amounts of alkene, added to or present in the reaction medium.⁵⁸⁸ The reaction involves addition of chromyl chloride to a carbon disulfide or carbon tetrachloride solution of the arene. A dark brown, insoluble and *explosive* intermediate usually precipitates. Dilute sulfurous acid is added to decompose the precipitate to the aldehyde. Toluene is converted to benzaldehyde and ethylbenzene was oxidized to phenylacetaldehyde with this reagent.

Chromyl chloride can also produce ketones, but formation of a α -chloro ketone is common, as in the conversion of cyclododecene to α -chlorocyclododecanone (**416**) in 79% yield.⁵⁸⁹ The chloride moiety in **416** was reduced with zinc and acetic acid in a subsequent reaction to give cyclododecanone in 95% yield. Alkenes react with chromyl chloride to give a trans-chlorohydrin rather than a carbonyl compound (see sec. 2.10.C for the preparation of chlorohydrins), as in the conversion of cyclohexene to *trans*-2-chlorocyclohexanol.⁵⁹⁰ It is interesting that when the temperature was maintained at -78° C in dichloromethane, the cischlorohydrin was formed.⁵⁹¹



Lead tetraacetate initiates oxidation with terminal alkenes in the presence of acid, to give an

- 589. Sharpless, K.B.; Teranishi, A.Y. J. Org. Chem. 1973, 38, 185.
- 590. Cristol, S.J.; Eilar, K.R. J. Am. Chem. Soc. 1950, 72, 4353.
- 591. (a) Sharpless, K.B.; Teranishi, A.Y.; Bäckvall, J.E. J. Am. Chem. Soc. 1977, 99, 3120; (b) Fieser, M. Reagents for Organic Synthesis Vol. 8 Wiley, New York, 1980, p 112.

^{584.} Reference 233a, pp 132-142.

^{585. (}a) Reference 233a, pp 140, 321; (b) Freeman, F.; DuBois, R.H.; Yamachika, N.J. Tetrahedron 1969, 25, 3441.

^{586. (}a)Reference 233a, p140; (b)Freeman, F.; DuBois, R.H.; McLaughlin, T.G. Org. Synth. Coll. Vol. 61988, 1028.

 ^{587. (}a) Étard, M.A. Compt. Rend. 1880, 90, 534; (b) Ferguson, L.N. Chem. Rev. 1946, 38, 227 (see p 237); (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-29.

^{588.} Tillotson, A.; Houston, B. J. Am. Chem. Soc. 1951 73, 221.
aldehyde by selective oxidation of the terminal carbon.⁵⁹² An example is the conversion of styrene to phenylacetaldehyde in 98% yield.⁵⁹³ Palladium chloride (PdCl₂) reacts with terminal alkenes, in the presence of oxygen and copper salts, to give a methyl ketone (this reaction is called the **Wacker process** which is discussed in sec. 12.6.A), and is more useful than the LTA oxidation. Oxidation of terminal alkenes with LTA leads to the aldehyde, whereas oxidation with PdCl₂ leads to the methyl ketone. The PdCl₂ oxidation of a terminal alkene to a methyl ketone is illustrated by conversion of **417** to **418**, in >80% yield, in Leighton and co-worker's synthesis of dolabelide D.⁵⁹⁴



Mercuric salts induce oxidative rearrangement of cyclic alkenes to give cycloalkane carboxaldehydes.⁵⁹⁵

Cyclohexene, for example, gave cyclopentane carboxaldehyde (**419**) in 53% yield.^{596,592} Acyclic alkenes such as 2-butene can also be oxidized with mercuric sulfate and sulfuric acid, giving 2-butanone in this case.⁵⁹⁷ Thallium nitrate $[Tl(NO_3)_3]$ is an important reagent for the oxidative rearrangement of cyclic alkenes.⁵⁹⁸ The reaction is not restricted to carbocyclic compounds, but can also be applied to heterocyclic compounds as shown by the oxidation of 3,4-dihydro-*2H*-pyran (**420**) to the dimethyl acetal (**421**) in 65% yield.⁵⁹⁹



The functional group transforms presented in this section are



^{592.} Reference 233a, p 136.

- 597. Charavel, B.; Metzger, J. Bull. Chim. Soc. Fr. 1968, 4102.
- 598. Reference 233a, pp 137-139.
- 599. McKillop, A.; Hunt, J.D.; Kienzle, F.; Bigham, E.; Taylor, E.C. J. Am. Chem. Soc. 1973, 95, 3635.

^{593.} Lethbridge, A.; Norman, R.O.C.; Thomas, C.B. J. Chem. Soc. Perkin Trans. 1 1973, 35.

^{594.} Park, P.K.; O'Malley, S.J.; Schmidt, D.R.; Leighton, J L. J. Am. Chem. Soc. 2006, 128, 2796.

^{595. (}a) Reference 233a, pp 135-136; (b) Arzoumanian, H.; Metzger, J. Synthesis 1971, 527.

^{596. (}a) Grummitt, O.; Liska, J.; Greull, G. Org. Synth. Coll. Vol. 5 1973, 320; (b) English, Jr., J.E.; Gregory, J.D.; Trowbridge II, J.R. J. Am. Chem. Soc. 1951, 73, 615.

3.9. OXIDATION OF SULFUR, SELENIUM, AND NITROGEN

It is possible to oxidize atoms other than carbon. Sulfur, selenium and nitrogen are easily oxidized by many of the oxidizing agents presented in this chapter. Several oxidation stages are available, leading to an interesting array of functional groups. Sulfur, for example, can be oxidized from a sulfide to a sulfoxide, which is turn can be oxidized to a sulfone. Sulfonic acids and sulfonate esters represent even higher oxidation states for sulfur. Selenium behaves similarly to sulfur. Nitrogen can be oxidized to hydroxylamines, nitrones, N-oxides or nitro compounds. These groups figure prominently in many synthetic transformations. In section 2.9.C, *N*-oxides, sulfoxides and selenoxides were important intermediates for syn-elimination reactions. In this chapter (sec. 3.5.B), *N*-oxides and sulfones will be used to stabilize carbanions, which react to form carbon-carbon bonds. It is therefore fitting that this chapter conclude with a brief survey of the methods for oxidizing these important synthetic intermediates.

3.9.A. Oxidation of Sulfur Compounds

$R^1 \overset{S}{\sim} R^2$	$R^1 \overset{O}{\overset{U}{\overset{U}{\overset{U}{\overset{U}{\overset{U}{\overset{U}{\overset{U}{$	$O_{R^1} O_{R^2} O_{R^2}$	3
422	423	424	i i

3.9.A.i. Oxidation of Sulfides to Sulfoxides. Sulfides (thioethers, 422) are readily oxidized to sulfoxides (423) by a variety of oxidizing agents, but sodium periodate (NaIO₄) is a convenient reagent. Further oxidation of sulfoxides

to sulfones (424) requires more vigorous conditions but is straightforward.⁶⁰⁰ Sulfides can be oxidized directly to the corresponding sulfoxide with peroxyacids, hydrogen peroxide or alkyl hydroperoxides. The overall mechanism for oxidations with peroxy acids and alkyl hydroperoxides is shown.⁶⁰⁰ In the reaction with peroxyacids, the sulfide attacks the O–O bond along an $S_N 2$ trajectory (see 425). The O–O bond is broken, and the hydrogen is transferred to the carbonyl group, liberating a carboxylic acid and the sulfoxide.⁵⁹⁹ This type of reaction with alkyl hydroperoxides usually requires acid catalysis. When the sulfide attacks the O-O bond of a hydroperoxide, hydrogen transfer liberates an alcohol and the acid catalyst, as shown in 426.⁶⁰⁰

^{600.} Reference 254, pp 244-247.

Sulfides react faster than alkenes with hydrogen peroxide and alkyl hydroperoxides. For this reason, transition metal catalysts are rarely necessary, but these reactions are acid catalyzed and first order in both sulfide and peroxide. The acid (HX) can be as weak as alcohol or water but the "effectiveness (of the oxidation) is determined by the pK_a of the acid."⁶⁰¹ Sulfides also react faster than ketones with peroxides (see the Baeyer-Villiger reaction, sec. 3.6). Formation of the sulfone in these reactions is straightforward, but this over-oxidation usually requires more vigorous reaction conditions. It is usually easy to isolate the sulfoxide from oxidation of a sulfide. Direct conversion of a sulfide to a sulfone requires excess peroxide and vigorous reaction conditions (heating, long reaction times, more concentrated peroxide).



Sodium meta-periodate (NaIO₄) is a common oxidizing agent. Leonard and Johnson used sodium periodate to oxidize methylphenyl sulfide to the sulfoxide in near-quantitative yield.⁶⁰² In that report, many

methods were summarized for oxidizing sulfides, including nitric acid, hydrogen peroxide, chromic acid, ozone, peroxyacids, manganese dioxide, and selenium dioxide.⁶⁰³ Sykes and Todd were apparently the first to use sodium periodate with sulfides, oxidizing benzylpenicillin

methyl ester (427) to the corresponding sulfoxide (428).⁶⁰⁴ Sodium periodate is often the reagent of choice for the oxidation of sulfides to sulfoxides, but mcpba can also be used as in the oxidation of sulfide 429 to sulfide 430.⁶⁰⁵



3.9.A.ii. Preparation of Chiral Sulfoxides. The sulfur atom in a sulfoxide has four different groups (R, R^1 , O, and the lone pair electrons). There is virtually no inversion at sulfur (in contrast to nitrogen) so the sulfur can be a stereogenic center under these circumstances, which raises two points when using unsymmetrical sulfoxides. When a stereogenic center is present

^{601.} Reference 254, p 245.

^{602.} Leonard, N.J.; Johnson, C.R. J. Org. Chem. 1962, 27, 282.

^{603. (}a) Märcker, C. Annalen 1865, 136, 75; (b) Reid, E.E. Organic Chemistry of Bivalent Sulfur, Vol. II, Chemical Pub. Co. Inc., New York, 1960, pp 64-66; (c) Bordwell, F.G.; Boutan, P.J. J. Am. Chem. Soc. 1957, 79, 717; (d) Gazdar, M.; Smiles, S. J. Chem. Soc. 1908, 93, 1833; (e) Hünig, S.; Boes, O. Annalen 1953, 579, 23; (f) Peak, D.A.; Watkins, Y.I. J. Chem. Soc. 1950, 445; (g) Edwards, D.; Stenlake, J.B. J. Chem. Soc. 1954, 3272; (h) Horner, L.; Schaefer, H.; Ludwig, W. Chem. Ber. 1958, 91, 75; (i) Overberger, C.G.; Cummins, R.W. J. Am. Chem. Soc. 1953, 75, 4250; (j) Barnard, D. J. Chem. Soc. 1956, 489; (k) Mel'nikov, N.N. Uspekhi Khim. 1936, 5, 443 [Chem. Abstr. 30: 51809 1936]; (l) Ford-Moore, A.H. J. Chem. Soc. 1949, 2126.

^{604. (}a) Sykes, P.; Todd, A.R., Committee on Penicillin Synthesis Report 526,677; (b) *The Chemistry of Penicillin*, Clarke, H.T.; Johnson, J.R.; Robinson, R.(Eds), Princeton Univ. Press, Princeton, N.J., *1949*, pp 156, 927, 946, 1008.

^{605.} Jiang, B. Chem. Commun. 1996, 861.

in a given molecule, incorporation of a sulfoxide moiety can lead to formation of diastereomers that can complicate separation and identification. The second point is that methods have been developed to resolve enantiomeric sulfoxides, or produce one enantioselectively, and use this material as a chiral auxiliary or as a chiral template (sec. 10.9).

Cram and Kingsbury reported an example that illustrates the oxidation of sulfides to sulfoxides with formation of diastereomers.⁶⁰⁶ Oxidation of erythro- or threo-1-alkylthio-1,2-diphenylpropane with peroxybenzoic acid gave syn- and anti- sulfides. The erythro-sulfide (anti-sulfide **431**) gave two erythro- (anti) sulfoxides, **432** and **433**.⁶⁰⁶ Similarly, the threo- sulfide (syn-sulfide **434**) gave two threo-(syn-sulfides, **435** and **436**. Both stereogenic carbons retain



their absolute configuration during the oxidation, but the oxygen is delivered to different faces of sulfur to generate the observed diastereomers. In general, the achiral A-S-B sulfide (**438**) is converted to the chiral sulfoxide **439**. When (+)-peroxycamphoric acid (**437**) was used, the configuration of the predominant optical isomer was the same as in **439** if A was bulkier than B. Later work by Folli et al. confirmed this preference.⁶⁰⁷ Approach of sulfur to the peroxyacid occurs in the direction of the lone pair of electrons on sulfur (an S_N2 like trajectory toward the O-O bond of the peroxide; *vide supra*) and can lead to either the (*R*) or the (*S*) enantiomer. As the difference between A and B became larger, or the chiral peroxyacid was made bulkier, greater selectivity was observed. The nature of the solvent influenced the observed optical yields (% ee), which were in the range of 1.2-4.5% ee.⁶⁰⁷ Oxidation of phenylmethyl sulfide with (+)-monoperoxycamphoric acid gave the chiral, nonracemic sulfoxide with a 1.2% ee in acetonitrile, and similar oxidation gave 1.7% ee in 2-propanol, 3.8% ee in chloroform, 4.5% ee in ether, 3.6% ee in benzene, and 3.1 % ee in dioxane.^{608,607}

^{606.} Kingsbury, C.A.; Cram, D.J. J. Am. Chem. Soc. 1960, 82, 1810.

^{607.} Folli, U.; Iarossi, D.; Montanari, F.; Torre, G. J. Chem. Soc. C 1968, 1317.

^{608. (}a) Mislow, K.; Green, M.M.; Raban, M. J. Am. Chem. Soc. 1965, 87, 2761; (b) Mislow, K.; Green, M.M.; Laur, P.; Melillo, J.T.; Simmons, T.; Ternay, Jr., A.L. Ibid. 1965, 87, 1958.



Many methods have been reported that generate chiral sulfoxides with high %ee.⁶⁰⁹ Kagan and Duñach⁶¹⁰ as well as DiFuria et al.,⁶¹¹ used titanium tetraisopropoxide $[Ti(OiPr)_4]$ and optically active diethyl tartrate (DET) to catalyze the reaction, analogous to the **Sharpless asymmetric epoxidation** discussed in section 3.4.D.i. DiFuria and co-workers oxidized benzylmethyl sulfide (**440**) to **441** in dichloromethane, in 46% ee.⁶¹¹ Kagan, Duñach, and co-workers oxidized methylphenyl sulfide to the corresponding (*S*)-sulfoxide in water with 89% ee under similar conditions.⁶¹⁰ Katsuki and Saito used a titanium-salen catalyst to obtain chiral sulfoxides with up to 96% ee.⁶¹²

Ph
$$\frown$$
 S⁻CH₃ $\xrightarrow{t-BuOOH, Ti(Oi-Pr)_4}$ Ph \frown S⁻
(+)-DET, CH₂Cl₂
-77*C, 24 h 441 CH₃

Davis et al. used a chiral oxaziridine for the asymmetric oxidation of sulfides to sulfoxides.⁶¹³ Oxidation of isopropyl-*p*-tolyl sulfide (**442**) with oxaziridine **443**, for example, gave 60.3% ee (S) of **444** (at –78°C in chloroform).⁶¹³ The absolute configuration of the sulfide is determined by approach of the sulfide to the oxaziridine oxygen, as illustrated by **445**. Steric factors appear to be the primarily reason for the chiral recognition.⁶¹⁴ In this model, attack by sulfur minimizes the R_L and R_s interactions with the oxaziridine moiety (R_s \Leftrightarrow SO₂R¹ and R_L \Leftrightarrow Ar or R_s \Leftrightarrow Ar and R_L \Leftrightarrow SO₂R¹). When R¹ in **445** is (+)-10-camphor, the resulting oxaziridine derivative reacted with sulfide to give the (+)-(*R*)-sulfoxide whereas the adduct derived from (–)-camphor gave the (–)-(*S*)-sulfoxide.⁵⁸⁰ Davis reported several other chiral oxaziridine reagents that gave good to excellent asymmetric induction for the oxidation of sulfides to sulfoxides. These regents are a mild and excellent alternative to oxidation using chiral peroxyacids.

- 611. DiFuria, F.; Modena, G.; Seraglia, R. Synthesis 1984, 325.
- 612. Saito, B.; Katsuki, T. Tetrahedron Lett. 2001, 42, 3873.

Smith, M.B. Compendium of Organic Synthetic Methods, Vol. 10, Wiley, NY, 2002, pp 231-236; Vol. 11, 2003, pp 474-476.

^{610. (}a) Pitchen, P.; Duñach, E.; Deshmukh, M.M.; Kagan, H.B. J. Am. Chem. Soc. **1984**, 106, 8188; (b) Pitchen, P.; Kagan, H.B. *Tetrahedron Lett.* **1984**, 25, 1049.

^{613.} Davis, F.A.; McCauley, Jr., J.P.; Chattopadhyay, S.; Harakal, M.E.; Towson, J.C.; Watson, W.H.; Tavanaiepour, I. J. Am. Chem. Soc. 1987, 109, 3370.

^{614. (}a) Davis, F.A.; Jenkins, Jr., R.H.; Awad, S.B.; Stringer, O.D.; Watson, W.H.; Galloy, J. J. Am. Chem. Soc. 1982, 104, 5412; (b) Davis, F.A.; McCauley, Jr., J.P.; Harakal, M.E. J. Org. Chem. 1989, 49, 1465.



3.9.A.iii. Oxidation of Sulfides or Sulfoxides to Sulfones and Oxidation of Selenium Compounds. The mechanism for the oxidation of sulfoxides to sulfones is probably similar to that for oxidation of sulfides,⁶¹⁵ but sulfoxides are less reactive than sulfides and the reaction slower.⁶¹⁶ Sulfoxides are oxidized to sulfones using the same oxidants that converted the sulfide to a sulfoxide, but longer reaction times and/or more vigorous conditions are usually required. Direct oxidation of a sulfide to a sulfone is also easily accomplished in many cases. Oxidation of sulfide 446 with mcpba gave sulfone 447 directly without oxidation of the sensitive pyrrole unit.⁶¹⁷ Note that the sulfur in a sulfone is achiral since there are two oxygen atoms.

$$\begin{array}{c|c} & & & \\ & & \\ & & \\ & & \\ & & \\ & H \\ & & \\$$

The selenium analogs of the sulfide, sulfoxide and sulfone are known, and the generic structures are **448**, **449**, and **450**, respectively. The oxidation of these compounds is virtually identical to those observed with sulfur. The main drawback to their use is the toxicity of the selenium compounds. Selenoxides are relatively unstable and decompose at ambient temperatures via syn-elimination. Selenoxide elimination is more facile than the analogous sulfoxide elimination (0°C versus 120°C), and is often preferred in organic synthesis (secs. 2.9.C.v, 2.9.C.vi). The thermal instability of selenoxides is also reflected in selenones, which are labile and rarely used.

$$\begin{array}{ccccccc} & & & & & O & & & O \\ R^{1-Se}-R^2 & & R^{1-Se}-R^2 & & R^{1-Se}-R^2 \\ & & & & & O \\ 448 & & 449 & & 450 \end{array}$$

^{615.} Reference 254, p 246.

^{616.} Boeseken, J.; Arrias, E. Rec. Trav. Chim. 1935, 54, 711.

^{617.} Miranda, L.D.; Cruz-Almanza, R.; Alvazez-García, A.; Muchowski, J.M. Tetrahedron Lett. 2000, 41, 3035.

3.9.B. Oxidation of Amines

The oxidation of nitrogen compounds is also common in organic chemistry. Aromatic nitro compounds are very important commercial compounds and their preparation was discussed in section 2.11.B. The reader is referred to the references found here and to specific applications for the preparation of oxides of nitrogen. Two categories of nitrogen compounds that are subject to oxidation are amines and amides. Amides "do not react well with hydrogen peroxide or peroxyacids, but most other nitrogen compounds react readily."⁶¹⁸ Oxidation of primary amines gives the nitroso (**452**) and the nitro compound (**453**) via the hydroxylamine derivative (**451**).⁶¹⁹ Ozonolysis of phosphinimines also produces nitro compounds.⁶²⁰ Secondary amines are also oxidized via the hydroxylamine (**454**) but eliminate to give the nitrone (**455**).

As mentioned above, nitro compounds are obviously of great importance in organic chemistry and aryl nitro compounds are an important source of aniline derivatives (secs. 4.2.C.v, 4.8.D). Both amine oxides and nitrones have been synthetically exploited. Alkyl nitroso derivatives, however, usually cannot be isolated since they decompose in solution, although the aromatic derivatives are more stable in solution and can be used in synthesis (sec. 2.11.E). Treatment of a primary amine with excess peroxyacid is a useful preparative route to alkyl nitro compounds.⁶²¹ Yields are highest for tertiary alkyl primary amines, then secondary followed by primary alkyl. Peroxyacid oxidation of oximes also provides a route to alkyl

nitro compounds.⁶²² This method is convenient for preparing aromatic nitro compounds as in the oxidation of 2,6-dichloroaniline to 2,6-dichloronitrobenzene (**456**).⁶²³ Nitrones are 1,3-dipoles and have been used in 1,3-dipolar cycloaddition reactions (sec. 11.11.D).



Tertiary amines give *N*-oxides directly and in high yield. Katritzky⁶²⁴ described the chemistry of heterocyclic *N*-oxides. Thermal elimination of N-oxides is the basis of the classical Cope reaction. (sec. 2.9.C.ii).⁶²⁵

^{618.} Reference 254, pp 248-253.

^{619.} Reference 254, p 250.

^{620.} Corey, E.J.; Samuelsson, B.; Luzzio, F.A. J. Am. Chem. Soc. 1984, 106, 3682.

^{621.} Emmons, W.D. J. Am. Chem. Soc. 1957, 79, 5528.

^{622.} Emmons, W.D.; Pagano, A.S. J. Am. Chem. Soc. 1955, 77, 4557.

^{623. (}a) Reference 433a, p 332; (b) Pagano, A.S.; Emmons, W.D. Org. Synth. Coll. Vol. 5 1973, 367.

^{624.} Katritzky, A.R. Quart. Rev. 1956, 10, 395.

^{625.} Cope, A.C.; Trumbull, E.R. Org. React. 1966, 11, 317.

3.10. CONCLUSION

This chapter focused on synthetically useful oxidation reactions for a variety of functional group transformations. This treatment is not comprehensive, but illustrates the various oxidation methods and reagents. These techniques will resurface in many syntheses and as part of other methodology in succeeding chapters. In Chapter 4, the reverse process, reduction, will be presented, emphasizing synthetically useful reactions and reagents.

HOMEWORK

1. The following reaction was reported in the synthesis of niphatoxin B. Give the product and suggest a mech-anistic rationale for this reaction.



2. The product of this reaction was expected to be a diol-acid, and the infrared (IR) showed an OH peak and a strong carbonyl, but there was no apparent CO₂H absorption. Likewise, the ¹H NMR showed there was no CO₂H group. Show the actual product and explain why the anticipated diol-acid was not isolated.

MOMO
$$(1)$$
 (1) (2)

- 3. Explain each of the following:
 - (a) The following reaction was reported in Paquette and Geng's synthesis of ceratopicanol. Explain the product as well as the stereochemistry of the alcohol unit.



(b) Explain the regioselectivity of this reaction.



(c) Explain why *p*-quinone is the major product.



(d) Explain why the nonconjugated alkene reacts preferentially.



4. Give the major product of each reaction and explain the regiochemistry and/or stereochemistry where applicable.



5. Predict the major product. Draw an appropriate transition state for each reaction.



6. (a) Identify each product (?) in the following sequence, taken from Taber's synthesis of (-)-fumagillin.



(b) Identify ?_a, ?_b, and ?_c in the following sequence, taken from Smith's synthesis of (+)-thiazinotrienomycin E.



(a) BuLi, ether-DMSO; MeI (b) O₃; PPh₃ (c) PDC, DMF

7. Briefly explain how the product shown is formed in this Swern oxidation, taken from Feldman and Saunders synthesis of (–)-agelastatin A.



8. Provide a mechanism to explain the following transformation.



9. Give the major product for each reaction.





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10. In each case, provide a suitable synthesis. Give all reagents that are necessary and show all intermediate products.











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chapter 4 Reduction

4.1. INTRODUCTION

Oxidation reactions were introduced in section 3.1 briefly reviewed. Reduction reactions are equally important, and many different classes of organic molecules can be reduced. If an oxidation reaction proceeds with an increase in oxidation state and a loss of electrons,¹ then a reduction reaction proceeds with a decrease in oxidation state and a gain of electrons. The concept of oxidation stage that was introduced in section 3.1 is also useful for reduction since reduction can be defined as conversion of an atom in a higher oxidation stage to a lower one (III \rightarrow II, IV \rightarrow II or II \rightarrow I), as in the transformation RCH=NH \rightarrow RCH₂NH₂.² The oxidation numbers of Holleran and Jespersen,³ and the modified method of Hendrickson, Cram, Hammond⁴ and Pine⁵ are useful for analyzing reduction reactions. It is also convenient to view organic reductions as the addition of hydrogen to the molecule. This latter definition is not always mechanistically correct, but it is conceptually useful and examples are the reduction of 2-butanone to 2-butanol or propanenitrile to butanamine.

$$\overbrace{O}^{+1} \underbrace{\text{gain 2 e^{-s}}}_{OH} \xrightarrow{\frown}_{OH}^{-1} C^{-1} \xrightarrow{+3} C^{-1} OH$$

As with oxidation (sec. 3.1), reduction potential can be used to assess the ability of a reagent to reduce molecules. The standard reduction potentials for several metals and metal salts commonly used in synthesis are available.⁶ For a metal to behave as a reducing agent, the reverse reaction (Li \rightarrow Li⁺, for example) must be facile. The high reduction potential of Li⁺ \rightarrow Li (-4.045 V)⁶ indicates that the Li \rightarrow Li⁺ reaction is favored, and lithium metal is an excellent reducing agent (by contrast, Li⁺ is a very poor oxidizing agent). Conversely, Sn⁴⁺ \rightarrow Sn²⁺ has a positive reduction potential (0.15 V)⁶ indicating a facile reaction. On the other hand, Sn²⁺ \rightarrow Sn[°] (-0.136 V)⁶ indicates that Sn²⁺ a reducing agent. The standard hydrogen electrode is taken as zero V, but this does not really represent the reducing power of hydrogen gas in the presence

^{1.} Yalman, R.G. J. Chem. Educ. 1959, 36, 215.

^{2.} Soloveichik, S.; Krakauer, H. J. Chem. Educ. 1966, 43, 532.

^{3.} Holleran, E.M.; Jespersen, N.D. J. Chem. Educ. 1980, 57, 670.

^{4.} Hendrickson, J.B.; Cram, D.J.; Hammond, G.S. Organic Chemistry, 3rd ed., McGraw-Hill, New York, 1970.

^{5.} Pine, S.H. Organic Chemistry, 5th ed, McGraw-Hill, New York, 1987.

^{6.} Handbook of Chemistry and Physics, 87th ed., CRC/Taylor and Francis, Boca Raton, Fla., 2006, pp 8-20-8-32.

of a suitable catalyst. The reduction potentials of hydride reducing agents are not usually listed, although they are among the most potent reducing agents. For these reasons, no attempt will be made to use reduction potentials to correlate the reducing power of each reagent.

Chapter 3 was organized by functional group changes, and the various reagents and techniques for each transformation were discussed. Most of the reduction techniques, despite their differences in mechanism and reagents, accomplish the same or similar functional group changes. There are, of course, differences in functional group reactivity as well as chemoselectivity and stereochemistry for the various reagents. This chapter is organized by type of reduction, with a discussion of applicable functional group transformations. The monograph on reduction by Hudlicky⁷ categorized reductions as reduction with complex hydrides, catalytic hydrogenation, electroreduction, reduction with metals, and reductions with non-metals. This excellent work includes an extensive survey of specific organic functional group reductions, to which the reader is referred for detailed information concerning reduction and reduction types. The order of topics in this chapter attempts to correlate a type of reduction with its relative utility in organic synthesis. This chapter will begin with hydride reductions since they are probably the most widely used, followed by catalytic hydrogenation. Reduction by various metals, including reduction by electrolysis and reduction with non-metals will follow. The final sections will deal with miscellaneous nonmetal reductions, including photoreduction and enzymatic or microbial reductions.

Reduction of prochiral centers (sec. 1.4.E) can generate enantiomers and diastereomers. It is therefore important to introduce the models that are used to predict the diastereoselectivity or enantioselectivity of a reduction. These stereochemical explanations are applicable to many reactions in organic chemistry, but it is important that stereoselectivity be viewed as a *part of the reaction* and **not** as a separate topic. For that reason, stereoselective reactions are discussed in each chapter where they are pertinent. It will be seen that reduction includes a wide range of functional group interchanges and important synthetic processes.

4.2. REDUCTION WITH COMPLEX METAL HYDRIDES

4.2.A. Lithium Aluminum Hydride

4 LiH + AlCl₃ $\xrightarrow{\text{ether}}$ LiAlH₄ + 3 LiCl 4 NaH + B(OMe)₃ \longrightarrow NaBH₄ + 3 MeO⁻ Na⁺

Gaylord's monograph with the title shown for this section⁸ as well as his contemporary review,⁹

^{7.} Hudlicky', M. Reductions in Organic Chemistry, Ellis Horwood Ltd., Chichester 1984.

^{8.} Gaylord, N.G. Reduction with Complex Metal Hydrides, Wiley-Interscience, New York 1956.

^{9.} Gaylord, N.G. J. Chem. Educ. 1957, 34, 367.

describes hydride reducing agents that were used until 1957. The two most common hydride reducing agents are lithium aluminum hydride (LiAlH₄) and sodium borohydride (NaBH₄, to be discussed in sec. 4.4).¹⁰ Schlesinger and co-workers, as well as Brown and co-workers,¹¹ reported the synthesis and initial applications of LiAlH₄ for reduction of organic compounds,¹² in 1947. Lithium aluminum hydride was prepared by reaction of lithium hydride (LiH) with aluminum chloride (AlCl₃).¹³ Sodium borohydride was first prepared by reaction of sodium hydride (NaH) with trimethylborate, B(OMe)₃.^{13,14}

Further studies showed that replacement of the hydrogen in LiAlH₄ or NaBH₄ with alkyl or alkoxy groups led to a variety of reducing agents with modified reducing abilities, chemoselectivity, and stereoselectivity. Lithium aluminum hydride is one of the most powerful reducing agents known for organic substrates bearing a polarizable functional group. This reagent is stable at ambient temperatures, but reacts violently with moisture to give hydrogen gas, lithium hydroxide and aluminum hydroxide (hydrated alumina), as shown:⁹

$$LiAlH_4 + 4H_2O \longrightarrow LiOH + Al(OH)_3 + 4H_2$$

The moisture does not have to be inadvertently added water. It can arise from "inadequately dried apparatus, fingerprints, and perspiration-soaked gloves", leading to ignition.¹⁵ Although this reagent is commercially available as a powder, lumps are also available. "Lumps are best crushed by cautious pounding with a hard rubber hammer in a tray with an aluminum foil liner. Grinding with a mortar and pestle should be done in a dry box in an atmosphere of nitrogen or argon.... If ground too vigorously in the presence of air the hydride may take fire."¹⁵ Theses quotations from Fieser emphasize the reactivity of LiAlH₄ and the danger of mishandling this reagent.

Lithium aluminum hydride has some solubility in ether solvents, but tends to form a slurry when relatively large amounts of the reagent are used. The solubility of LiAlH₄ in ether is 35-40 g/100 g of ether, but obtaining this solubility requires concentration of a more dilute solution.¹⁴ The solubility is 13g/100 g in THF and 0.1 g in dioxane,¹⁴ which are also commonly used solvents. The reagent is usually represented as $Li^+[AlH_4^-]$ and exists as aggregates of solvated lithium ions and aluminohydride ions in diethyl ether.¹⁶ Such slurries of LiAlH₄ are capable of reducing virtually all polarized organic functional groups, as described by Gaylord.^{9,8}

For a review of 60 years of hydride reductions, see Brown, H.C.; Ramachandran, P.V.. in *Reductions in Organic Synthesis. Recent Advances and Practical Applications*, Abdel-Magid, A.F (Ed.), ACS Symposium Series 641, American Chemical Society, Washington, DC, *1996*. pp 1-30.

^{11.} Nystrom, R.F.; Brown, W.G. J. Am. Chem. Soc. 1947, 69, 1197.

^{12.} Finholt, A.E.; Bond, A.C.; Schlesinger, H.I. J. Am. Chem. Soc. 1947, 69, 1197.

^{13.} Reference 7, p 14.

^{14.} Schlesinger, H.I.; Brown, H.C.; Finholt, A.E. J. Am. Chem. Soc. 1953, 75, 205.

^{15.} Fieser, L.F.; Fieser, M. Reagents for Organic Synthesis Vol. 1, Wiley, New York 1967, pp 581-595.

^{16.} House, H.O. *Modern Synthetic Reactions, 2nd ed,* Benjamin, Menlo Park CA, *1972*, p 49 and citations 5, 12 and 14 therein.

Molecules with an acidic hydrogen such as acids, alcohols, amines, etc. may react with lithium aluminum hydride in an acid-base reaction to generate hydrogen gas with destruction of the active hydride.

4.2.B. Reduction of Carbonyl Compounds

Lithium aluminum hydride rapidly reduces most carbonyl compounds, including aldehydes and ketones,¹⁷ carboxylic acids, acid anhydrides, acid chlorides, esters, lactones, amides, carbamates, imides, and lactams.¹⁸ Most LiAlH₄ reductions of carbonyl compounds begin by coordination to the carbonyl oxygen, followed by transfer of the nucleophilic hydride (oxygen is polarized δ - relative to aluminum) to the electrophilic carbonyl (carbon is polarized δ + relative to oxygen). House illustrated this mechanism for the LiAlH₄ reduction of acetone, showing the stepwise formation of alkoxyaluminate intermediates.¹⁶ Initial transfer of hydride to the carbonyl generates **2**, possibly via direct coordination of aluminum to oxygen and transfer of hydride to the carbonyl carbon. Complex **1** has also been proposed as an intermediate. Alkoxide **2** contains three additional active hydrides, so a second equivalent of carbonyl can react to give bis(alkoxide) **3**. Similarly, a third equivalent gives **4** and a fourth gives **5**.

The reactivity of each new hydride intermediate with the carbonyl substrate decreases with the increasing number of electronegative alkoxy substituents.¹⁵ It is not always obvious how many carbonyl units add to LiAlH₄ for a given substrate. In principle, one molar equivalent of acetone reacts with four equivalents of hydride (which is 1/4 mole of LiAlH₄) to give **5** (R = Me). A very bulky ketone such as 2,4-dimethyl-3-pentanone (diisopropyl ketone) gives a different result, reacting with LiAlH₄ to give **2** or **3** (R = *i*-Pr). Addition of the carbonyl compound to LiAlH₄ (a 1:1 molar ratio), followed by titration of the complex with water or aqueous acid will release hydrogen gas from the unreacted hydrides. The hydrogen gas can be trapped, allowing an exact determination of the number of carbonyl molecules that reacted with the tetrahydroaluminate. In general, at least one molar equivalent (four equivalents of H⁻)

^{17.} Larock, R.C. Comprehensive Organic Transformations, 2nd ed, Wiley-VCH, New York, 1999, p 1077.

^{18.} For reagents used to reduce acid derivatives, see Reference 17, pp 1263-1273.

or more are added to the carbonyl moiety to ensure complete reduction. A complicating factor is that alkoxyaluminate intermediates are subject to disproportionation, as in the reversible interconversion of **6** to **7**,^{16,19} which is more of a problem with increasing steric bulk around the carbonyl carbon (ketone > aldehyde; 2° carbon > 1° carbon). Disproportionation regenerates the tetrahydroaluminate anion, which can cause overreduction as well as loss of functional group specificity, and stereoselectivity.¹⁶

$$2 \qquad \begin{array}{c} 2 \qquad \begin{array}{c} 0 \\ - 0 \\ H \\ H \end{array} \qquad \begin{array}{c} 0 \\ - 1 \\ H \end{array} \qquad \begin{array}{c} 0 \\ - 1 \\ - 1 \\ H \end{array} \qquad \begin{array}{c} 0 \\ - 1 \\ - 1 \\ H \end{array} \qquad \begin{array}{c} 0 \\ - 1 \\ - 1 \\ H \\ - 1 \\ H \end{array} \qquad \begin{array}{c} 0 \\ - 1 \\ - 1 \\ H \\ - 1 \\ - 1 \\ H \end{array} \qquad \begin{array}{c} 0 \\ - 1 \\$$

The final alcohol product from the reduction of $R_2C=O$ is generated by treatment of **5** (or any other alkoxyaluminate product) with aqueous acid or with aqueous base via protonation of the alkoxide base. In many cases, titration with water is sufficient to release the alcohol but saturated ammonium chloride or dilute hydrochloric acid is sometimes necessary. Aqueous or acidic workup of a LiAlH₄ reaction is exothermic and evolves hydrogen gas, which leads to frothing. Since volatile ether solvents are usually employed, isolation of the alcohol can be difficult and sometimes dangerous with large scale reactions. If excess water is added, the alumina salts formed during the hydrolysis can form a paste that is difficult to filter. Fieser and Fieser described^{20a} the basic workup procedure of Mićović and Mhailović's,^{20b,c} which has several advantages. It produces a granular precipitate that is easily filtered [for *n* grams of LiAlH₄ *n* mL of water, then *n* mL of 15% NaOH followed by 3*n* mL of water]. Although this information is best found in a lab manual, in fact, the choice of a reducing agent is often dictated by the relative ease of isolation of a given product and this discussion is offered with that in mind.

The rate of reduction of aldehydes is faster than that of ketones, because there is less steric hindrance for delivery of hydride to the carbonyl carbon. In extreme cases, reduction of highly hindered ketones may have a half-life that measures in days, but rarely does reduction fail to occur. This observation stands in contrast to results obtained with other reducing agents such as sodium borohydride²¹ (sec. 4.4), which reduces only selected functional groups. A typical synthetic use of this reaction is reduction of the aldehyde moiety in **8**, which gave a 92% yield of alcohol **9** in Wiemer and co-worker's synthesis of schweinfurthin B.²²

^{19. (}a) Kader, M.H.A. Tetrahedron Lett. 1969, 2301; (b) Eliel, E.L.; Senda, Y. Tetrahedron 1970, 26, 2411.

 ⁽a) Reference 15, p 584 (b) Mićović, V.M.; Mhailović's, M.L. J. Org. Chem. 1953, 18, 1190.; (c) Amundsen, L.H.; Nelson, L.S. J. Am. Chem. Soc. 1951, 73, 242.

^{21.} Brown, H.C.; Ichikawa, J. J. Am. Chem. Soc. 1962, 84, 373.

^{22.} Treadwell, E.M.; Neighbors, J.D.; Wiemer, D.F. Org. Lett. 2002, 4, 3639.



One of the more important characteristics of carbonyl reduction with $LiAlH_4$ is the diastereoselectivity of the reaction when reduction introduces a second stereogenic center. As a general rule, hydride is delivered to the less sterically hindered face of the molecule *unless* special chelation or coordination effects are present. We will present a detailed discussion of this concept in section 4.7.

Reduction of α , β -unsaturated carbonyl derivatives poses a potential problem. Reduction of benzalacetone (**10**) can lead to either the allylic alcohol (**11**) via normal 1,2-addition of hydride to the carbonyl, or to the saturated alcohol (**12**) via 1,4-reduction (delivery of hydride to the alkenyl carbon).²³ Initial 1,2-reduction leads to a bis(alkoxyaluminate) (**13**), which is apparently converted to an intermediate such as **14**.²⁴ If reduction proceeds via coordination



of the aluminum to the carbonyl oxygen (represented by generalized model 16) 1,2-reduction occurs via path *a* (to give 15), which is the usual pathway (see $1 \rightarrow 2$). The β -carbon in 16 is polarized with a positive dipole, however, and hydride can also be delivered to the β -carbon via path *b* (a six-center transition state). This path leads to conjugate (1,4) addition, and enolate 17 is the product. If the R group in 16 is small (e.g., hydrogen in conjugated aldehydes), 1,2-addition predominates. As the R¹ and/or R² groups increase in size, delivery to the β -carbon is sterically inhibited (giving more 15). Conjugate reduction is common for α , β -unsaturated ketones when the β -carbon is relatively unhindered. Conjugate reduction is rare for conjugated aldehydes, although there are a few reagents that give this product in high yield (see the discussion for aluminum hydride in sec. 4.6.B). House pointed out that 14 is

^{23. (}a) Reference 7, p 171, 179 and citations 29 and 158 therein (pp. 313, 316); (b) Meek, J.S.; Lorenzi, F.J.; Cristol, S.J. J. Am. Chem. Soc. **1949**, 71, 1830.

^{24.} Reference 16, pp 89-90.

subject to disproportionation, or that another mechanism may be operative in this reduction.²⁴ Inverse addition of the hydride (a slurry of LiAlH₄ is added to the carbonyl compound), short reaction times, and low reaction temperatures generally give moderate to good yields of the conjugate reduction product.²⁴ Good yields of allylic alcohols can often be obtained from α , β -unsaturated aldehydes, however, when the reaction is done at low temperatures with strict control of the stoichiometry.



Reduction of carboxylic acids with one equivalent of LiAlH₄ consumes three of the four,²⁵ and the reduction product is an alcohol. The acidic hydrogen of the COOH unit reacts first. Subsequent reduction of the carbonyl unit leads to the alkoxyaluminate, which is hydrolyzed to the alcohol. In Passaro and Webster's synthesis of the female sex pheromone of the citrus mealybug, *Planococcus citri*, acid **18** was reduced to alcohol **19**.²⁶ Reduction of acids bearing a heteroatom at the α -position gives the corresponding alcohol.



LiAlH₄ reduces acid derivatives, including acid chlorides, esters or amides. Reduction of the highly reactive acid chlorides¹² and acid anhydrides²⁷ is rapid. Partial reduction of aromatic anhydrides²⁸ to lactones has been reported by controlling the stoichiometry of LiAlH₄ and the anhydride. In most cases, however, complete reduction to the diol occurs.^{27,12,28}

Reduction of esters (RCO₂R') to hydroxymethyl derivatives (RCH₂OH) along with the alcohol unit R'OH proceeds without loss of stereochemistry at the α -carbon of the ester. Reduction of the *tert*-butyl ester group **20** gave alcohol **21** in 91% yield after hydrolysis (the silyl enol ether moiety was hydrolyzed to the ketone simultaneously), taken from a synthesis of myrmicarin 215A by Movassaghi and Ondrus.²⁹ A common application that focuses on the R'OH unit is the reduction of acetates, which give the corresponding alcohol (RCH₂OAc \rightarrow RCH₂OH) along with ethanol.

26. Passaro, L.C.; Webster, F.X. J. Agric. Food Chem. 2004, 52, 2896.

29. Movassaghi, M.; Ondrus, A.E. Org. Lett. 2005, 7, 4423.

^{25.} Reference 8, p 322.

^{27.} Reference 8, p 375 and citation 105 cited therein (p 389).

^{28. (}a) Mahé, J.; Rollet, J.; Willemart, A. Bull. Chim. Soc. Fr. 1949, 16, 481; (b) Ratouis, R.; Willemart, A. Compt. Rend. 1951, 233, 1124.



The ester moiety of readily available amino esters (derived from amino acids) can be reduced to give chiral amino alcohols, which have a variety of uses in synthesis.³⁰ The 1,2-reduction of conjugate esters leads to allylic alcohols under the proper reaction conditions. 1,4-Reduction of conjugated esters is often a problem, as it is with conjugated aldehydes and ketones, but selective 1,2-reduction is easily attained as shown by the conversion of **22** to **23** in >55% yield in Wiemer and co-worker's synthesis of (2E,6Z)-farnesol.³¹



The reduction of cyclic esters (lactones) leads to diols, as in the reduction of δ -valerolactone to give an 85% yield of 1,5-pentanediol.³² The size of the lactone ring is determined by the number of carbons separating the hydroxyl units.³³ Stereogenic centers adjacent to the oxygen and carbonyl of the lactone³⁴ are not compromised during the reduction. The conformational bias of the lactone ring can be used to control the relative stereochemistry of substituents as they are incorporated on the ring (Chap. 6). In a synthesis of (–)-enterodiol by Eklund and co-workers, lactone **24** was reduced to diol **25** in 71% yield.³⁵ When the lactone carbonyl is sterically hindered as in **26**, partial reduction is possible. In this case, lactol **27** was formed in > 80% yield.³⁶ In general, however, partial reduction of lactones with LiAlH₄ is *difficult* and one normally expects that LiAlH₄ reduction will give a diol.

- 32. Nystrom, R.F.; Brown, W.G. J. Am. Chem. Soc. 1948, 70, 3738.
- 33. Lal, K.; Salomon, R.G. J. Org. Chem. 1989, 54, 2628.
- 34. Corey, E.J.; Ishiguro, M. Tetrahedron Lett. 1979, 2745.
- 35. Eklund, P.; Lindholm, A.; Mikkola, J.-P.; Smeds, A.; Lehtilä, R.; Sjöholm, R. Org. Lett. 2003, 5, 491.
- 36. Venkataraman, H.; Cha, J.K. J. Org. Chem. 1989, 54, 2505.

 ⁽a) Coppola, G.M.; Schuster, H.F. Asymmetric Synthesis: Construction of Chiral Molecules Using Amino Acids, Wiley, New York 1987; (b) Smith, M.B. Methods of Non-α-Amino Acid Synthesis, Marcel Dekker, New York, 1995.

^{31.} Yu, J.S.; Kleckley, T.S.; Wiemer, D.F. Org. Lett. 2005, 7, 4803.



Amides do not give alcohol products upon hydride reduction, in contrast to other acid derivatives. Reaction of an amide with LiAlH₄ initially gives an intermediate iminium salt, which is further reduced to an amine as the final product. Oxygen is completely removed from the molecule, as illustrated in a synthesis of communesin B by Funk and Crawley,³⁷ in which amide **28** was reduced to amine **29** in 92% yield. Initial transfer of hydride to the amide forms a complex such as **30**. Further reduction and subsequent elimination of the alkoxyaluminate gives an iminium salt (**31**), and additional hydride (as in **32**) and hydrolysis gives the amine.³⁸ Increased steric hindrance on nitrogen makes coordination and delivery of hydride more difficult. Although uncommon, C–N bond cleavage can occur to give an aldehyde and the products are an alcohol and an amine. Aldehyde formation is observed when the electron-donating ability of the nitrogen is diminished by substituents, but yields are generally poor.



Reduction of derivatives is an effective method for the monomethylation or dimethylation of amines. Reaction of 2-phenylethanamine with formaldehyde and formic acid gave the reactive

^{37.} Crawley, S.L.; Funk, R.L. Org. Lett. 2003, 5, 3169.

^{38.} Reference 8, pp 544-546.

intermediate iminium salt **33**, which was reduced by formic acid to the *N*-methyl derivative (**34**). In this particular example, **34** was subjected to further reaction with formaldehyde and reduction led to dimethylamino product **35** in 83% yield.³⁹ A related reaction is the reduction of benzamide derivatives (easily prepared by reaction of an amine with benzoyl chloride or bromide) to *N*-benzyl derivatives.⁴⁰ Reduction of an imide usually proceeds with cleavage to give an amine and an alcohol.

$$\begin{array}{c} Ph \\ NH_2 \end{array} \xrightarrow{2 \text{ HCHO}} \left[\begin{array}{c} H \\ Ph \\ \hline 2 \text{ HCO}_2H \end{array} \right] \left[\begin{array}{c} H \\ Ph \\ \hline 33 \end{array} \right] \xrightarrow{} \left[\begin{array}{c} H \\ Ph \\ \hline N - CH_3 \end{array} \right] \xrightarrow{} Ph \\ \hline 34 \end{array} \right] \xrightarrow{} Ph \\ \begin{array}{c} H_3C \\ Ph \\ \hline 35 \end{array}$$

Carbamates are characterized by a O–CO–N group with an electron withdrawing ester unit on the nitrogen. Amines are easily converted to carbamates (sec. 7.3.C.iii) and reduction provides a useful method for the synthesis of methylamines.⁴¹ Indeed, amides and carbamates are common precursors to alkylamines. In Correia and co-worker's synthesis of paroxetine, both the methyl ester and the methyl carbamate units in **36** were reduced with LiAlH₄ to give the hydroxymethyl group and the *N*-methylamine **37**, respectively, in 56% yield after hydrolysis.⁴² It is also possible to focus on reduction of the alcohol portion of the carbamate. Reduction of a benzyl carbamate gives a benzylic alcohol, for example (this is called a Cbz protecting group; see sec. 7.3.C.iii).⁴³



Lactams are cyclic amides, and are reduced by LiAlH₄ to the corresponding cyclic amine. The reduction of a typical lactam such as 2-pyrrolidinone derivative **38**, presumably proceeds via initial formation of the α -amino alcohol (**39**) followed by elimination to an iminium salt (**40**) and then reduction by hydride to give the amine (**41**). A synthetic example is the reduction of lactam **42** to crispine A (**43**) in 76% yield, in Allin and co-workers synthesis of (*R*)-(+)-crispine A.⁴⁴

- 41. Baxter, E.W.; Labaree, D.; Chao, S.; Mariano, P.S. J. Org. Chem. 1989, 54, 2893.
- 42. Pastre, J.C.; Duarte Correia, C.R. Org. Lett. 2006, 8, 1657.

^{39.} Icke, R.N.; Wisegarver, B.B.; Alles, G.A. Org. Synth. Coll. Vol. 3 1955, 723.

^{40.} Hunt, J.H.; McHale, D. J. Chem. Soc. 1957, 2073.

^{43.} Reference 8, p 636.

^{44.} Allin, S.M.; Gaskell, S.N.; Towler, J.M. R.; Page, P.C.B.; Saha, B.; McKenzie, M.J.; Martin, W.P. J. Org. Chem. 2007, 72, 8972.



Conjugated amides can undergo both 1,2- and 1,4-addition with hydrides, but there is a competing side reaction. Reductive coupling is possible via generation of an intermediate amide enolate.⁴⁵ Reduction of the relatively hindered *N*,*N*-diethyl-3,3-dimethylacrylamide (44) gave a 47% yield of the expected conjugate reduction product 45, but also 12% of the enolate condensation product 46.⁴⁵ Enolate condensations will be discussed in Chapter 9.



With the exception of amides, it is clear that the principal reduction product of carbonyl derivatives is an alcohol. Succeeding sections will discuss the reduction products observed for functional groups that do not contain a carbonyl group. The functional group transforms for this section include:



4.2.C. Lithium Aluminum Hydride Reduction of Non-Carbonyl Heteroatom Functional Groups

As shown by Gaylord,⁸ lithium aluminum hydride reduces heteroatom-containing functional groups. This section will explore the reduction of several functional groups that are commonly seen in synthesis.

^{45.} Snyder, H.R.; Putnam, R.E. J. Am. Chem. Soc. 1954, 76, 1893.

4.2.C.i. Epoxides. Epoxides are easily generated from alkenes⁴⁶ (sec. 3.4), and also from ketones and aldehydes⁴⁷ (sec. 8.8.B). They are one of the most useful of all oxygenated functional groups and reduction of epoxides leads to alcohols.⁴⁸ Lithium aluminum hydride usually delivers hydride with excellent selectivity to the less substituted carbon of an epoxide.⁴⁹ An example is taken from the Yamamoto and co-worker's synthesis of α -bisabolol,⁵⁰ where reduction of the epoxide unit in **47** gave alcohol **48** in 93% yield. When the epoxide oxygen can coordinate with the aluminum (via an *ate* complex), epoxides can give products where ydride is delivered to the more substituted carbon.⁵¹ Intramolecular delivery of hydride is to the most electropositive carbon, although intermolecular delivery is also possible.⁵²



4.2.C.ii. Ozonides. Ozonolysis is a powerful method for cleaving alkenes to carbonyl products (sec. 3.7.B). Ozonolysis of alkenes initially generates an ozonide that can be reduced by a variety of reagents. Dimethyl sulfide or zinc in acetic acid are the most common reagents for the reduction of an ozonide to an aldehyde or ketone. Reduction of the ozonide with the more powerful LiAlH₄, however, gives direct the alcohol directly.

4.2.C.iii. Nitriles. Nitriles are synthetic precursors for both functional group transformation and carbon-carbon bond forming reactions (secs. 8.2, 9.4.B.iv). They are usually formed by a S_N2 substitution reaction in which cyanide displaces a leaving group from an alkyl halide or sulfonate ester, or by dehydration of amides (secs. 2.6.A.i, sec. 8.2). Once the nitrile has been formed reduction of the cyano group with LiAlH₄ usually gives a primary amine,⁵³ so nitriles function as protected (latent) aminomethyl groups. This transformation is seen in a synthesis of (–)-tubifoline by Mori and co-workers,⁵⁴ in which the nitrile unit in **49** was reduced to an aminomethyl unit in **50** using LiAlH₄. The amine product is sometimes trapped (protected,



^{46.} Lewis, S.N. in Oxidation, Vol. 1, Augustine, R.L. (Ed.), Marcel Dekker, New York 1969, p223.

- 47. Trost, B.M.; Melvin, Jr., L.S. Sulfur Ylides, Academic Press, New York, 1975.
- 48. For reagents used to reduce epoxides and other cyclic ethers, see Reference 17, p 1019.
- 49. Reference 8, p 653.
- 50. Makita, N.; Hoshino, Y.; Yamamoto, H. Angew. Chem. Int. Ed. 2003, 42, 941.
- 51. Azuma, H.; Tamagaki, S.; Ogino, K. J. Org. Chem. 2000, 65, 3538.
- 52. Reference 16, p 104.
- 53. For reagents used to reduce nitriles, see Reference 17, p 1271.
- 54. Mori, M.; Nakanishi, M.; Kajishima, D.; Sato, Y. J. Am. Chem. Soc, 2003, 125, 9801.

sec. 7.3.C) by reaction with an acyl halide to give an amide, since this allows further synthetic manipulation. Nitrile reduction by hydride proceeds via initial formation of an iminium salt (**51**) and subsequent conversion to a bis(iminoaluminate), **52**.⁵⁵ The literature is rather vague concerning the specific structure of **52**, but reduction with additional hydride leads to **53** as reported by Soffer and Katz.⁵⁵ The hydrogen atoms in the amine product probably come from hydrolysis, although the nature and substitution pattern of the nitrogen in **53** was not specified. The aluminum moiety in **53** may be coordinated by a solvent molecule (usually ether or THF) or a second aluminum species. In some cases, removal of the α -proton occurs to give the α -lithio nitrile (sec. 9.4.B.iv),⁵⁵ especially when a hydride slurry is added to the nitrile solution (inverse addition). A dimeric product is formed that is indicative of an enolate condensation. Addition of butanenitrile to lithium aluminum hydride gave butanamine in 79%, for example, but inverse addition in ether gave only 34% of that amine. Inverse addition also led to 26% of 2-ethyl-1,3-hexanediamine, presumably via a **Thorpe condensation**⁵⁶ (sec. 9.4.B.iv) of an intermediate nitrile carbanion.⁵⁵

$$\mathbb{R} \xrightarrow{\operatorname{AlH}_{4^{-}}} \left[\begin{array}{c} \mathbb{R} \xrightarrow{} & -\overline{\operatorname{AlH}_{3}} \end{array} \right] \xrightarrow{\operatorname{RCH}_{2}\operatorname{CN}} \left[\left(\begin{array}{c} \mathbb{R} \xrightarrow{} & N \end{array} \right) \xrightarrow{} \overline{\operatorname{AlH}_{4^{-}}} \\ \mathbb{H} \end{array} \right] \xrightarrow{\operatorname{AlH}_{4^{-}}} \left[\left(\begin{array}{c} \mathbb{R} \xrightarrow{} & N \end{array} \right) \xrightarrow{} \overline{\operatorname{AlH}_{3}} \right] \xrightarrow{\operatorname{H}_{3}\operatorname{O}^{+}} \xrightarrow{\operatorname{R}} \\ \mathbb{H} \xrightarrow{} & N \operatorname{H}_{2} \end{array} \right] \xrightarrow{\operatorname{AlH}_{4^{-}}} \left[\left(\begin{array}{c} \mathbb{R} \xrightarrow{} & N \end{array} \right) \xrightarrow{} \overline{\operatorname{AlH}_{3}} \right] \xrightarrow{\operatorname{H}_{3}\operatorname{O}^{+}} \xrightarrow{\operatorname{R}} \\ \mathbb{H} \xrightarrow{} & N \operatorname{H}_{2} \end{array} \right] \xrightarrow{\operatorname{AlH}_{4^{-}}} \left[\left(\begin{array}{c} \mathbb{R} \xrightarrow{} & N \end{array} \right) \xrightarrow{} \overline{\operatorname{AlH}_{3}} \right] \xrightarrow{\operatorname{AlH}_{4^{-}}} \\ \mathbb{H} \xrightarrow{} & \mathbb{H} \xrightarrow{} & \mathbb{H} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} & \mathbb{H} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} & \mathbb{H} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \xrightarrow{} \\ \mathbb{H} \xrightarrow{} \\ \mathbb{$$

4.2.C.iv. Azides. Azides are important precursors to amines.⁵⁷ The azide anion (N_3^-) is an excellent nucleophile and $S_N 2$ displacement of primary and secondary halides (or alkyl sulfonates) with sodium azide (sec. 2.6.A.i) gives the corresponding alkyl azide. Reduction of the azido group with LiAlH₄ gives a primary amino group (R–N₃ \rightarrow R–NH₂). An example is taken from the Enders and Müller-Hüwen synthesis of D-*erythro*-sphinganine,⁵⁸ in which reduction of the azide group in **54** gave amine **55** in 99% yield (>96% ee).



4.2.C.v. Nitro Compounds. Aliphatic nitro compounds can be reduced to amines,⁵⁹ so they also function as amine surrogates. Reduction of nitriles or azides is usually the preferred method to introduce an amino group since reactions that introduce the nitro group often require strong acid. Aromatic nitration (sec. 2.11.B) is relatively easy, however, and reduction to aniline derivatives would be a very attractive synthetic route to this important class of amines.

^{55.} Soffer, L.M.; Katz, M. J. Am. Chem. Soc. 1956, 78, 1705.

 ⁽a) Baron H.; Remfry, F.G.P.; Thorpe, Y.F. J. Chem. Soc. 1904, 85, 1726; (b) Schaefer, J.P.; Bloomfield, J.J. Org. React. 1967, 15, 1.

^{57.} See Reference 17, p 815.

^{58.} Enders, D.; Müller-Hüwen, A. Eur. J. Org. Chem. 2004, 1732.

^{59.} See Reference 17, p 821.

Hydride reduction is not straightforward because LiAlH₄ reduction of nitrobenzene does not give aniline but rather azo compound **56** in 84% yield.⁶⁰ Catalytic hydrogenation (see sec. 4.8.D) is the best method for the reduction of aromatic nitro compounds to aniline derivatives. Aliphatic nitro compounds are relatively easy to reduce with LiAlH₄. The nitro group in **57** was cleanly reduced to give amine **58** as part of Scanlon and co-worker's synthesis of thyronamines.⁶¹ Note that in this case **57** is a conjugated nitro compound, and both the C=C and the NO₂ units were reduced.



4.2.C.vi. Alkyl Halides. Alkyl halides are reduced by lithium aluminum hydride to give a hydrocarbon in what is known as a **hydrogenolysis** reaction ($R_3C-X \rightarrow R_3C-H$; sec. 4.8.E).⁶² Reduction of 1-bromobutane in ether, THF or di-*n*-butyl ether gave yields of *n*-butane in the 30-96% range.^{63,32} A synthetic example is taken from the synthesis of (+)-clavosolide A by Lee and co-workers, in which reduction of the primary bromide moiety in **59** gave the corresponding methyl group in 96% yield (see **60**).⁶⁴ Benzylic halides⁶⁵ are relatively easy to reduce with LiAlH₄, when compared to simple aliphatic halides. Electronic effects can influence the yield. The presence of aryl groups leads to more facile reduction, as in the reduction of trityl chloride [Ph₃C–Cl] to triphenylmethane [Ph₃C–H] in 98% yield. Simple aryl halides are resistant to reduced (40% yield of chlorobenzene was obtained upon reaction with LiAlH₄). Electron-releasing groups such as methyl or methoxy enhance the yield of reduction products.⁶⁷ Hydride reduction of allylic halides is sometimes plagued by reductive elimination as a competitive side reaction.



^{60.} Hart, M.E.; Suchland, K.L.; Miyakawa, M.; Bunzow, J.R.; Grandy, D.K.; Scanlan, T.S. J. Med. Chem. 2006, 49, 1101.

- 61. Ohta, H.; Kobayashi, N.; Ozaki, K. J. Org. Chem. 1989, 54, 1802.
- 62. See Reference 17, p 779.
- 63. Rassat, A.; Ravet, J.P. Bull. Soc. Chim. Fr. 1968, 3679.
- 64. Son, J.B.; Kim, S. N.; Kim, N.Y.; Lee, D.H. Org. Lett. 2006, 8, 661.
- 65. Trevoy, L.W.; Brown, W.G. J. Am. Chem. Soc. 1949, 71, 1675.
- 66. Reference 8, pp 917-922.
- 67. Feutrill, G.I.; Mirrington, R.N.; Nichols, R.J. Aust. J. Chem. 1973, 26, 345.

4.2.C.vii. Sulfonate Esters. Sulfonate esters are readily formed by reaction of alcohols with sulfonyl halides and are reduced to the hydrocarbon with LiAlH₄, via cleavage of the C–O bond.⁶² Reaction of the primary alcohol group in **61** with tosyl chloride generated the tosylate, and subsequent reduction with LiAlH₄ led to hydrogenolysis of the C–O bond to give **62** in 66% yield, as part of Harrity and co-worker's synthesis of (–)-nupharolutine.⁶⁸ Reduction of sulfonate esters commonly gives yields below 50%, and alkyl sulfonate groups are similarly reduced with LiAlH₄.⁶⁹ Indeed, cleavage of the C–O bond in primary tosylates (–CH₂OTs) or mesylates (–CH₂OMs) to a methyl group may be the most common application.^{70,71} Formation of an alcohol (via S–O bond cleavage) is often observed when the C–O bond is sterically hindered, accounting for the low yields mentioned above.



4.2.C.viii. Sulfonamides. Reduction of sulfonamides does *not* give an alcohol and an amine. Primary sulfonamides resist reductive cleavage with LiAlH₄; secondary sulfonamides are cleaved, but the reaction requires a temperature of 120°C in dibutyl ether.⁷² Exceptions to this sluggish reactivity occur when the sulfonamide is conjugated to a carbonyl moiety. Oppolzer et al. developed a chiral sulfonamide auxiliary (**Oppolzer's sultam 63**) derived from camphor,⁷³ and attachment of this auxiliary allows high asymmetric induction in a variety of reactions. In a synthesis of fumagillin by Perlmutter and co-workers, **63** was acylated and converted to **64** in five steps.⁷⁴ Reductive cleavage of the sulfonamide with lithium aluminum hydride removed the auxiliary in low yield to give alcohol **65** along with the auxiliary **63**, which could be recycled. Note that complete removal of this group is sometimes a problem, which can severely limit the utility of this auxiliary.

^{68.} Goodenough, K.M.; Moran, W.J.; Raubo, P.; Harrity, J.P.A. J. Org. Chem. 2005, 70, 207.

^{69.} For an example taken from a synthesis of chrysotricine, see Zhang, J.-X.; Wang, G.-X.; Xie, P.; Chen, S.-F.; Liang, X.-T. *Tetrahedron Lett.* **2000**, *41*, 2211.

^{70.} Rossi, R.; Salvadori, P.A. Synthesis 1979, 209.

^{71.} Fronza, G.; Fuganti, C.; Grasselli, P.; Marinoni, G. Tetrahedron Lett. 1979, 3883.

^{72. (}a) Searles, S.; Nukina, S. Chem. Rev. 1959, 59, 1077; (b) Klamann, D. Monatsh Chem. 1953, 84, 651.

^{73.} Oppolzer, W.; Chapuis, C.; Bernardinelli, G. Helv. Chim. Acta 1984, 67, 1397.

^{74.} Ciampini, M.; Perlmutter, P.; Watson, K. Tetrahedron: Asymmetry 2007, 18, 243.



4.2.C.ix. Alkyne-Alcohols. Formation of an alcohol in the presence of another functional group via reduction can sometimes lead to elimination to an alkene. This elimination process can be turned to an advantage when propargylic alcohols are reduced.⁷⁵ The so-called **Whiting reaction**⁷⁶ reduces an alkynyl diol such as **66** with LiAlH₄ to give a diene (**67**, cosmene) via addition of four hydrogen atoms followed by formal elimination of two equivalents of water. In general, LiAlH₄ does not reduce alkene or alkynyl moieties, but as noted in the Whiting reaction, propargylic alcohol derivatives (C=C-CH₂-OH) are important exceptions.^{77,78} Reduction of alkynyl alcohols, readily formed via condensation of alkyne anions with aldehydes and ketones (sec. 8.3.C), generally gives the trans-allylic alcohol as seen in a synthesis of leucascandrolide A by Carreira and Fettes,⁷⁹ in which propargyl alcohol **68** was reduced to **69** and converted to the benzoate ester in 90% overall yield.



This specialized reduction is not limited to C=CCHOH systems. Lithium aluminum hydride in refluxing diglyme also reduces homoallylic alkynyl alcohols (C=CCH₂CH₂OH). An example is the reduction of 3-decyn-1-ol (**70**) to dec-3*E*-en-1-ol (**71**) in 93% yield, as reported in Vyvyan

^{75.} Karlsen, S.; Frøyen, P.; Skattebøl, L. Acta Chem. Scand. 1976, 30B, 664; (b) Brown, H.C.; McFarlin, R.F. J. Am. Chem. Soc. 1956, 78, 252.

^{76. (}a) Nayler, P.; Whiting, M.C. J. Chem. Soc. 1954, 4006; (b) Isler, O.; Montavon, M.; Rüegg, R.; Zeller, P. Helv. Chim. Acta 1956, 39, 454; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-100.

^{77.} Reference 8, pp 968-975.

^{78.} Trost, B.M.; Lee, D.C. J. Org. Chem. 1989, 54, 2271.

^{79.} Fettes, A.; Carreira, E.M. J. Org. Chem. 2003, 68, 9274.

and co-worker's synthesis of gibbilimbol A.80

$$C_{6}H_{13} \xrightarrow{\qquad OH \qquad } OH \qquad \xrightarrow{1. \text{ LiAlH}_{4}, \text{ diglyme}} C_{6}H_{13} \xrightarrow{\qquad OH \qquad } OH \qquad \qquad \\ \hline 2. \text{ hydrolysis} \qquad \qquad \hline 71$$

The functional group transforms in this section are summarized as

$$\begin{array}{c} R \xrightarrow{R} & \bigcap_{OH} O R \xrightarrow{R} & R \cdot NH_2 \stackrel{\circ}{\bigcirc} R \cdot N_3 \stackrel{\circ}{\bigcirc} R \cdot X \xrightarrow{R} \xrightarrow{R} \stackrel{R^1}{\bigcirc} \stackrel{R^2}{\bigcirc} \stackrel{R^1}{\bigcirc} \stackrel{R}{\longrightarrow} \stackrel{R^1}{O} \stackrel{R}{\longrightarrow} \stackrel{R^1}{OH} \stackrel{R}{\longrightarrow} \stackrel{R^1}{OH} \stackrel{R}{\longrightarrow} \stackrel{R^1}{OH} \stackrel{R}{\longrightarrow} \stackrel{R^1}{OH} \stackrel{R}{\longrightarrow} \stackrel{R^1}{OH} \stackrel{R}{\longrightarrow} \stackrel{R^1}{OH} \stackrel{R}{\longrightarrow} \stackrel{R}{\longrightarrow} \stackrel{R^1}{OH} \stackrel{R}{\longrightarrow} \stackrel{R}{\longrightarrow} \stackrel{R}{\longrightarrow} \stackrel{R}{OH} \stackrel{R}{\longrightarrow} \stackrel{R}$$

4.3. ALKOXYALUMINATE REAGENTS

Lithium aluminum hydride is a powerful reducing agent that can reduce many functional groups, and it is common for the reduction to span several oxidation stages ($-CO_2Et \rightarrow -CHO \rightarrow -CH_2OH$, for example). There are many instances when a single oxidation stage reduction is desirable (such as $-CO_2Et \rightarrow -CHO$), without overreduction. Selective reduction of one functional group in the presence of others is also important, because multifunctional molecules may contain several reducible functional groups (i.e., lactone + ester + aldehyde). In such a system, lithium aluminum hydride could reduce all of them. An example of this poor selectivity is the reduction of **72** to **73**, in which the ketone, cyano and ester groups were reduced at $-78^{\circ}C$ (95% yield) in Heathcock and co-worker's synthesis of fawcettimine.⁸¹ A chemoselective (a term introduced by Trost) reduction will reduce a single functional group in high yield, in the presence of the other functional groups. This section will examine reagents that exhibit chemoselectivity for selected functional groups.



Is it possible for a reagent to react faster with one functional group than with another? The answer *may* be yes in some cases, but in **72**, reaction with $LiAlH_4$ rapidly reduced all three functional groups so any rate differences were probably imperceptible. If the hydride reagent were structurally modified so that its reducing power was diminished, however, small

^{80.} Vyvyan, J.R.; Holst, C.L.; Johnson, A.J.; Schwenk, C.M. J. Org. Chem. 2002, 67, 2263.

^{81.} Heathcock, C.H.; Blumenkopf, J.A.; Smith, K.A. J. Org. Chem. 1989, 54, 1548.

differences in rates of reduction for various functional groups might be exploited, allowing selective reduction of one functional group in the presence of another. It was shown previously that reaction of lithium aluminum hydride with carbonyls led to alkoxyaluminates, and that each successive reaction with the carbonyl was slower. This is consistent with the observation that the alkoxyaluminates are increasingly less reactive as more OR units replace H in the aluminate. As long as an Al–H unit remains in the molecule, that alkxovaluminate is a reducing agent. Alkoxyaluminates such as $LiAlH_n(OR)_{4-n}$ can be prepared by the direct reaction of lithium aluminum hydride with an appropriate alcohol. Addition of *n* equivalents of ROH leads to the alkoxyaluminate with 4-n H remaining on aluminum. Brown showed that many alcohols could be used to prepare alkoxyaluminum hydrides. Four equivalents of methanol, for example, reacted with LiAlH₄ to form lithium tetramethoxyaluminum [LiAl(OMe)₄], but three equivalents (in ether, THF, or glyme) gave LiAlH(OMe)₃ [lithium trimethoxyaluminum hydride].⁸² Similarly, three equivalents of ethanol gave lithium triethoxyaluminum hydride, LiAlH(OEt)₃. Brown first showed that treatment of LiAlH₄ with four equivalents of the hindered tert-butanol led to the release of only three equivalents of hydrogen gas (i.e., only three equivalents of hydride reacted), generating lithium tri-tert-butoxy aluminum hydride, LiAlH(Ot-Bu)₃.⁸³ This hydride failed to react with the excess *tert*-butyl alcohol at ambient temperatures (although it did react upon prolonged heating at elevated temperatures).⁸³ This reagent is significantly less reactive than LiAlH₄ or the other alkoxyaluminum hydrides. Brown went further, and compared the reducing power of lithium aluminum hydride, lithium tri-tert-butoxyaluminum hydride and lithium trimethoxyaluminum hydride with a variety of functional groups.⁸⁴ Lithium trimethoxyaluminum hydride is about as strong a reducing agent as lithium aluminum hydride.⁸⁵ Although the solid reagent is stable and sold commercially, ether solutions are not very stable. It is often preferable to prepare the reagent as needed, by addition of methanol to a THF slurry of lithium aluminum hydride.⁸⁵ Reduction of epoxides, nitriles, and tosylates was slow and nitriles gave mixtures of amines and aldehydes in poor yield.⁸⁶ Lithium triethoxyaluminum hydride is also unstable in solution and is usually prepared *in situ* by addition of three equivalents of ethanol to LiAlH₄ in ether at 0°C.⁸⁵ This powerful reducing agent showed good selectivity for reduction of nitriles and amides. Both aliphatic nitriles (such as isobutyronitrile) as well as aromatic nitriles are reduced to aldehydes in good yield.⁸⁶ Tertiary amides such as N.N-dimethylbutanamide, shown in the reaction, are also reduced to the aldehyde (in this case butanal).⁸⁷ As the steric bulk of the alkyl groups attached to the nitrogen of a tertiary amide increased, the yield of aldehyde was diminished. Reduction of the *N*,*N*-diethyl- analog of this amide, for example, gave only 47% of the aldehyde and reduction

^{82.} Brown, H.C.; Shoaf, C.J. J. Am. Chem. Soc. 1964, 86, 1079.

^{83.} Brown, H.C.; McFarlin, R.F. J. Am. Chem. Soc. 1958, 80, 5372

^{84.} Brown, H.C.; Yoon, N.M. J. Am. Chem. Soc. 1966, 88, 1464.

^{85.} Brown, H.C.; Weissman, P.M. J. Am. Chem. Soc. 1965, 87, 5614.

^{86.} Brown, H.C.; Garg, C.P. J. Am. Chem. Soc. 1964, 86, 1085.

^{87.} Brown, H.C.; Tsukamoto, A. J. Am. Chem. Soc. 1964, 86, 1089.

of the *N*,*N*-diisopropyl- analog gave no aldehyde.⁸⁷ Trimethoxyaluminum hydride and LiAlH₄ gave significantly lower yields of aldehydes with both nitriles and tertiary amides.

$$\begin{array}{c} \searrow C = N \xrightarrow{1. \text{ LiAlH(OEt)}_3} \\ 2. \text{ H}_3\text{O}^+ \end{array} \begin{array}{c} \searrow C\text{HO} \\ 0 \end{array} \xrightarrow{NNe_2} \\ 0 \end{array} \xrightarrow{1. \text{ LiAlH(OEt)}_3} \\ 0 \end{array} \xrightarrow{NN-\text{dimethylbutanamide}} \\ N.N-\text{dimethylbutanamide} \end{array}$$

Alkoxyaluminates are relatively mild reducing agents the can reduce the carbonyl of a lactone to give a lactol. In one example, **75** (an intermediate in Magnus and Hobbs' synthesis of grandisol)⁸⁸ was isolated in 97% yield by reduction of **74** with lithium triethoxyaluminum hydride at -20° C. Trialkoxyaluminum hydrides reduce aldehydes, ketones, esters and acid chlorides before reducing nitriles and amides.



Both lithium diethoxyaluminum hydride [LiAlH₂(OEt)₂]⁸⁹ and [LiAlH₃(OEt)],⁹⁰ lithium ethoxyaluminum hydride have been used in syntheses, but LiAlH(Ot-Bu)₃ is used more often. This latter reagent is stable in solution, gives useful concentrations in ether solvents (36 g/100g of THF, 2 g/100 g of diethyl ether, and 41 g/100 g of diglyme),⁸³ and reacts with organic substrates faster in solutions where it is in higher concentration. It is thermally stable and heating to 165°C for five hours followed by titration with acid showed that 92% of its active hydrogen was retained.⁸³ Although lithium tri-*tert*-butoxyaluminum hydride is less reactive than the other alkoxyaluminum hydrides discussed above, it easily reduces aldehydes, ketones, some esters, anhydrides or acid chlorides. Epoxides are reduced very slowly, and nitriles and dimethyl amides are not reduced at all. The use of this reagent is a preferred method for the selective reduction of acid chlorides to aldehydes. The best yields of the aldehyde is realized from aromatic acid chlorides, as in the reduction of *p*-nitrobenzoyl chloride to *p*-nitrobenzaldehyde in 80% yield.⁸³ The yield of aldehyde from aliphatic acyl chlorides is generally in the 40-60% range. Alkyl esters do not react, allowing some selectivity for the reduction of ketones and aldehydes in the presence of esters and other functional groups. Deprés, Greene, and co-workers reduced the ketone moiety in 76 to alcohol 77 in 83% yield with excellent diastereoselectivity, and without reduction of the lactone unit, in a synthesis

 ⁽a) Hobbs, P.D.; Magnus, P.D. J. Chem. Soc. Chem. Commun. 1974, 856; (b) Hobbs, P.D.; Magnus, P.D. J. Am. Chem. Soc. 1976, 98, 4594.

^{89.} Schwarz, M.; Oliver, J.E.; Sonnet, P.E. J. Org. Chem. 1975, 40, 2410.

 ⁽a) Morizur, J.P.; Bidan, G.; Kossanyi, J. *Tetrahedron Lett.* 1975, 4167; (b) Bidan, G.; Kossanyi, J.; Meyer, V.; Morizur, J.-P. *Tetrahedron* 1977, 33, 2193.

of homogynolide B.⁹¹ Although alkyl esters are generally unreactive with this reagent, many phenyl esters are reduced to the aldehyde, as in the conversion of methyl *p*-chlorobenzoate to *p*-chlorobenzaldehyde (-22° C, 8 h) in 77% yield.⁹² The presence of the *p*-chloro unit undoubtedly enhanced the reactivity.



Reaction of conjugated carbonyls with LiAlH(O*t*-Bu)₃ gives primarily 1,2-reduction, as in the quantitative reduction of **78** to **79** in Marshall and Ruth's synthesis of globulol.⁹³ Both sulfonate esters such as the mesylate group in **78**, and halides⁹⁴ are resistant to reduction with LiAlH(O*t* Bu)₃.



Sodium *bis*(2-methoxyethoxy)aluminum hydride (Red-Al[®], Vitride[®]) was prepared by Vit in 1967.⁹⁵ It was prepared in benzene, as shown, under a hydrogen atmosphere at temperatures $> 100^{\circ}$ C,⁹⁵ and its reducing power is close to that of lithium aluminum hydride. An important advantage of this reagent is its stability to dry air (it does not ignite in even moist air or oxygen), and it is thermally stable up to 200°C unlike LiAlH₄, which can detonate at elevated temperatures. Perhaps the greatest utility of Red-Al is its solubility in aromatic hydrocarbon and ether solvents, which allows it to be conveniently used for applications that require inverse addition of hydrides.

2 MeO
$$H$$
 $H^{Na^{+}}$ MeO H^{-} H

- 93. Marshall, J.A.; Ruth, J.A. J. Org. Chem. 1974, 39, 1971.
- 94. For a synthetic example, see Daniewski, A.R.; Kiegel, J. J. Org. Chem. 1988, 53, 5534.
- (a) Fieser, L.F.; Fieser, M. Reagents for Organic Synthesis Vol. 2, Wiley, New York, 1969, p382; (b) Fieser, L.F.; Fieser, M. Reagents for Organic Synthesis Vol. 3, Wiley, New York, 1972, p260; (c) Vit, J.; Cásensky, B.; Machácek, J. French Patent, 1,515,582 1968 [Chem. Abstr. 70: 115009x, 1967].

^{91.} Brocksom, T.J.; Coelho, F.; Deprés, J.-P.; Greene, A.E.; Freire de Lima, M.E.; Hamelin, O.; Hartmann, B.; Kanazawa, A.M.; Wang, Y. J. Am. Chem. Soc. 2002, 124, 15313.

^{92.} Weissman, P.M. Brown, H.C. J. Org. Chem. 1966, 31, 283.

The reactivity profile of Red-Al is essentially the same as LiAlH₄, reducing aldehydes, ketones⁹⁶ and acid derivatives to alcohols. Ketones and aldehydes are reduced with Red-Al at -78° C to the alcohol.⁹⁷ The analogy to LiAlH₄ reduction also applies to the reduction of carboxylic acids.⁹⁸ Reduction of conjugated carbonyls gives primarily 1,2-reduction to an allylic alcohol,⁹⁹ as in the reduction of **80** to **81** (80% yield) in the synthesis and structure elucidation of azaspiracid-1 by Nicolaou and co-workers.¹⁰⁰ Red-Al reduces esters to alcohols in a manner identical with LiAlH₄.¹⁰¹ The selectivity for 1,2-reduction can be changed to selectivity for 1,4-reduction by the addition of cuprous bromide (CuBr) to Red-Al, as in the conversion of **82** \rightarrow **83** in 72% yield.¹⁰² The active reducing agent is probably copper hydride. It is well known that addition of cuprous salts (Cu⁺) promotes conjugate addition (see organocuprates in sec. 8.7.A.vi).¹⁰³ Reaction of cuprous bromide (CuBr) and Red-Al gave a sodium complex whereas reaction of CuBr and LiAlH(OMe)₃ gave a lithium complex.^{104,105}



Other functional groups can be reduced, such as epoxides to alcohols,¹⁰⁶ and lactams to amines.¹⁰⁷ Epoxides are reduced at the less hindered carbon,¹⁰⁸ but the product distribution can vary with

- 98. Zurflüh, R.; Dunham. L.L.; Spain, V.L.; Siddall, J.B. J. Am. Chem. Soc. 1970, 92, 425.
- (a) Markezich, R.L.; Willy, W.E.; McCarry, B.E.; Johnson, W.S. J. Am. Chem. Soc. 1973, 95, 4414; (b) McCarry, B.E.; Markezich, R.L.; Johnson, W.S. Ibid. 1973, 95, 4416.

- 101. Avery, M.A.; Jennings-White, C.; Chong, W.K.M. J. Org. Chem. 1989, 54, 1789.
- 102. Bestmann, H.J.; Schmidt, M. Tetrahedron Lett. 1986, 27, 1999.
- 103. Paquette, L.A.; Schaefer, A.G.; Springer, J.P. Tetrahedron 1987, 43, 5567.
- 104. Semmelhack, M.F.; Stauffer, R.D.; Yamashita, A. J. Org. Chem. 1977, 42, 3180.
- 105. (a) Vedejs, E.; Fedde, C.L.; Schwartz, C.E. J. Org. Chem. 1987, 52, 4269; (b) Negishi, E.; Akiyoshi, K. Chem. Lett. 1987, 1007.
- For an example taken from a synthesis of (-)-8-O-methyltetrangomycin (MM 47755), see Kesenheimer, C.; Groth, U. Org. Lett. 2006, 8, 2507.
- 107. For an example taken from a synthesis of (-)-ibogamine, see White, J.D.; Choi, Y. Org. Lett. 2000, 2, 2373.
- 108. (a) Gao, Y.; Sharpless, K.B. J. Org. Chem. 1988, 53, 4081. For an example taken from a synthesis of δ-trans-tocotrienoloic acid, see (b) Maloney, D.J.; Hecht, S.M. Org. Lett. 2005, 7, 4297.

^{96.} Čapka, M.; Chvalovský, V.; Kochloefl, K.; Kraus, M. Collect. Czech. Chem. Commun. 1969, 34, 118.

^{97.} Stotter, P.L.; Friedman, M.D.; Minter, D.E. J. Org. Chem. 1985, 50, 29.

Nicolaou, K.C.; Pihko, P.M.; Bernal, F.; Frederick, M.O.; Qian, W.; Uesaka, N.; Diedrichs, N.; Hinrichs, J.; Koftis, T.V.; Loizidou, E.; Petrovic, G.; Rodriquez, M.; Sarlah, D.; Zou, N.J. Am. Chem. Soc. 2006, 128, 2244.

the solvent, especially when the steric hindrance is similar at each carbon of the epoxide. As with LiAlH₄, Red-Al reduces aromatic nitriles to amines, although aliphatic nitriles typical are difficult to reduce and give poor yields.¹⁰⁹ There are some

interesting differences in selectivity, relative to LiAlH₄. Cyanohydrin **84**, for example, was reduced to α -hydroxy-aldehyde **85**,¹¹⁰ rather than to the amino-methyl compound obtained with lithium aluminum hydride.



Hydrogenolysis of C–X bonds is usually faster than with LiAlH₄, and Red-Al is preferred to LiAlH₄ for reduction of aliphatic halides and many aromatic halides.¹¹¹ Primary aliphatic monohalides are reduced to the hydrocarbon (1-bromoheptane was reduced to heptane, for example, in 99% yield).¹¹¹ Aromatic halides are also reduced, as in the conversion of bromobenzene to benzene in 99% yield.¹¹¹ Under similar conditions, however, chlorobenzene gave only 15% of benzene. Selective mono-reduction is possible when more than one halide

is present. Reduction of the *gem*-dibromide moiety in **86**, for example, gave the syn-monobromide (**87**) as the major product.¹¹²

Sulfonate esters are reduced via C–O cleavage, as with LiAlH₄. Primary tosylates and mesylates are reduced to the methyl derivative.¹¹³ Sterically hindered sulfonate esters often give significant amounts of S–O cleavage during the reduction. Although LiAlH₄ does not readily reduce sulfonamides to the corresponding amine (sec. 4.2.C.viii, *vide supra*),¹¹⁴ cleavage of the N–S bond

with Red-Al is facile, as in the conversion of N-tosyl deoxyephedrine (88) to deoxyephedrine (89) in 64% yield.¹¹⁴ It was assumed that the sulfonate fragment lost from nitrogen in sulfonamide 88 was reduced to the thiol.



Red-Al can reduce benzylic alcohols to the hydrocarbon at elevated temperatures. The reaction occurs more readily when the aromatic ring contains an electron releasing group in the orthoor para-position, but the temperatures required can be $> 140^{\circ}$ C.¹¹⁵ Even at higher reaction temperatures, reduction to the alcohol can compete with formation of the hydrocarbon, but usually as a minor process. An amino group at a benzylic position is subject to hydrogenolysis. Reduction of 4-(*N*,*N*-dimethyl-amino)benzaldehyde with Red-Al at 141°C gave a mixture of

^{109.} Černý, M.; Málek, J.; Čapka, M.; Chvalovský, V. Collect. Czech. Chem. Commun. 1969, 34, 1033.

^{110.} Schlosser, M.; Brich, Z. Helv. Chim. Acta 1978, 61, 1903.

^{111.} Čapka, M.; Chvalovský, V. Collect. Czech. Chem. Commun. 1969, 34, 3110.

^{112.} Sydnes, L.; Skattebøl, L. Tetrahedron Lett. 1974, 3703.

^{113.} Zobačová, A.; Hermánková, V.; Jarý J. Collect. Czech. Chem. Commun. 1977, 42, 2540.

^{114.} Gold, E.H.; Babad, E. J. Org. Chem. 1972, 37, 2208.

^{115.} Černý, M.; Málek, J. Tetrahedron Lett. 1969, 1739.
4-hydroxymethyl-*N*,*N*-dimethylaniline (63% yield) and 4-methyl-*N*,*N*-dimethylaniline (8%).¹¹⁶ Similar reduction of 4-aminoacetophenone gave only toluidine, however, in 90% yield.¹¹⁶ As with LiAlH₄, propargylic alcohols are reduced to allylic alcohols.^{117,118}

Red-Al behaves as a base in certain applications, *if* a readily reducible functional group is *not* present in the molecule. Kametani used Red-Al to induce a **Steven's rearrangement** (sec. 8.8.C.ii) of berbine methiodide (**90**) to spirobenzylisoquinoline (**91**) (9.4%) plus **92** (22.5%).¹¹⁹ The yield of rearranged products was poor, which is typical for this application of Red-Al.



The functional group transforms most useful with Red-Al are:



4.4. **REDUCTIONS WITH BOROHYDRIDE**¹²⁰

4.4.A. Sodium Borohydride

Schlesinger and Brown first prepared sodium borohydride (NaBH₄) in 1943,¹²¹ but experimental details were not reported until the 1950s.¹²² Its discovery predated that of lithium aluminum hydride, but the security regulations of World War II (NaBH₄ was important for the separation of uranium salts as part of the Manhattan project) delayed its disclosure.¹²² Sodium borohydride is less reactive than lithium aluminum hydride so it is a selective reagent, often reducing

^{116.} Černý, M.; Málek, J. Collect. Czech. Chem. Commun. 1970, 35, 1216.

 ^{117. (}a) Mayer, H.J.; Rigassi, N.; Schwieter, U.; Weedon, B.C.L. *Helv. Chim. Acta* 1976, 59, 1424; (b) Kienzle, F.; Mayer, H.; Minder, R.E.; Thommen, W. *Ibid.* 1990, 524.

^{118.} Jones, T.K.; Denmark, S.E. Org. Synth. Coll. Vol. 7 1985, 64, 182.

^{119.} Kametani, T.; Huang, S-P.; Koseki, C.; Ihara, M.; Fukumoto, K. J. Org. Chem. 1977, 42, 3040.

^{120.} For a review of selective reductions using boron reagents, see Burkhardt, E.R.; Matos, K. Chem. Rev. 2006, 106, 2617.

^{121. (}a) Reference 15, p 1049; (b) Schlesinger, H.I. Brown, H.C. U.S. Patent 2,461,661, 2,461,663 [*Chem. Abstr.* 43: 4684e, 4684i **1949**; U.S. Patent 2,534, 533 [*Chem. Abstr.* 45: 4007i, **1951**].

^{122.} Schlesinger, H.I.; Brown, H.C.; Hoekstra, H.R.; Rapp, L.R. J. Am. Chem. Soc. 1953, 75, 199.

aldehydes, ketones or acid chlorides in the presence of other reducible functional groups.¹²³ The diminished reactivity is reflected in the solvents used for the reduction. Aqueous and alcohol solvents are preferred due to the excellent solubility of sodium borohydride (25 g/100 g of water at 0°C [88.5 g/100 g at 60°C], 16.4 g /100 g of methanol, 4g /100 g of ethanol).^{121a} Sodium borohydride reacts with water to form hydroxyborohydride intermediates, but these are also mild reducing agents. Similar reaction with alcohols is relatively slow so the most common reaction solvents are ethanol and 2-propanol. Sodium borohydride is relatively insoluble in ether solvents (0.1 g/100 g of THF, 5.5 g/100 g of diglyme and 0.8 g/100 g of DME), so these are rarely used for borohydride reductions. In most cases aqueous ammonium chloride, aqueous acetic acid, or dilute mineral acids are used for hydrolysis.

Ethanolic solutions of sodium borohydride reduce aldehydes and ketones in the presence of epoxides, esters, lactones, acids, nitriles or nitro groups.^{121a,124} In Cook and co-worker's synthesis of 6-oxoalstophylline,¹²⁵ reduction of the aldehyde moiety in **93** gave alcohol **94** in 95% yield. Sodium borohydride often gives the 1,2-reduction product from conjugated carbonyl derivatives, particularly when the terminal carbon of the conjugated system is sterically hindered. In general, sodium borohydride is an excellent reagent for the reduction of ketones or aldehydes in the presence of esters,¹²⁶ hydroxyl groups that are α to the carbonyl,⁴¹ a carbohydrate residue,¹²⁷ or halogens in the α position.¹²⁸ Aryl ketones¹²⁹ or aryl aldehydes¹³⁰ are also easily reduced.



Unconjugated ketones and aldehydes are usually reduced in preference to a conjugated carbonyl elsewhere in the molecule. Paquette and co-workers treated **95** with NaBH₄ and obtained **96** in good yield, without reduction of the conjugated ketone unit, as part of a synthesis of magellanine.¹³¹ Similar reduction with LiAlH₄ would reduce both carbonyl groups and give a mixture of 1,2- and 1,4-reduction products from the conjugated ketone.

- 123. Chaikin, S.W.; Brown, W.G. J. Am. Chem. Soc. 1949, 71, 122.
- 124. (a) Brown, H.C.; Krishnamurthy, S. *Aldrichimica Acta* 1979, 12, 3; (b) Schenker, R. *Angew. Chem.* 1961, 73, 81.
- 125. Liao, X.; Zhou, H.; Wearing, X. Z.; Ma, J.; Cook, J.M. Org. Lett. 2005, 7, 3501.
- 126. Kelley, R.C.; Schletter, I. J. Am. Chem. Soc. 1973, 95, 7156.
- 127. Ohrui, H.; Emoto, S. Agric. Biol. Chem. 1976, 40, 2267.
- 128. (a) De Amici, M.; De Micheli, C.; Carrea, G.; Spezia, S. J. Org. Chem. 1989, 54, 2646; (b) Gensler, W.J.; Solomon, P.H. J. Org. Chem. 1973, 38, 1726.
- 129. Burka, L.T.; Wilson, B.J.; Harris, T.M. J. Org. Chem. 1974, 39, 2212.
- 130. Dai-Ho, G.; Mariano, P.S.; J. Org. Chem. 1988, 53, 5113.
- 131. Williams, J.P.; St. Laurent, D.R.; Friedrich, D.; Pinard, E.; Roden, B.A.; Paquette, L.A. J. Am. Chem. Soc. 1994, 116, 4689.



Sodium borohydride reduces ozonides to an alcohol,¹³² just as LiAlH₄ was used in section 4.2.C.ii. An example is the ozonolysis of **97** where borohydride reduction gave alcohol **98** in 94% yield in a synthesis of (–)-cytoxazone by Jung and co-workers.¹³³



An important use of sodium borohydride is reduction of enamines, imines or iminium salts, which is particularly useful in alkaloid and amino acid syntheses. In a synthesis of (+)-majvinine,¹³⁴ Cook and co-workers converted the amine unit in **99** to the imine (**100**) by reaction with benzaldehyde. Subsequent reduction with NaBH₄ gave a 92% overall yield of the *N*-benzylamine, **101**. Enamines can also be reduced, as in Werner and co-worker's synthesis of opioid antagonists that used sodium borohydride to selectively reduce enamine **102** to **103**.¹³⁵



An important variation is called **reductive amination**, in which an aldehyde or ketone is mixed with an amine in the presence of sodium borohydride, generating the corresponding

^{132.} Johnson, C.R.; Senanayake, C.H. J. Org. Chem. 1989, 54, 735.

^{133.} Kim, J.D.; Kim, I.S.; Jin, C.H.; Zee, O.P.; Jung, Y.H. Org. Lett. 2005, 7, 4025.

^{134.} Zhao, S.; Liao, X.; Wang, T.; Flippen-Anderson, J.; Cook, J.M. J. Org. Chem. 2003, 68, 6279.

^{135.} Werner, J.A.; Cerbone, L.R.; Frank, S.A.; Ward, J.A.; Labib, P.; Tharp-Taylor, R.W.; Ryan, C.W. J. Org. Chem. 1996, 61, 587.

N-alkyl amine. Guillou and co-workers¹³⁶ used this technique in a synthesis of maritidine, where the reaction of aldehyde **104**, primary amine **105** and sodium borohydride gave a 78% yield of **106**. Pyridinium salts can also be reduced, illustrated by the conversion of **107** to **108** (haliclamine A) as the final step in that synthesis by Al-Mourabit and co-worker's.¹³⁷ In this reaction, initial reduction of each pyridinium salt generated a dienamine, and 1,2-reduction gave the final product, **108**.



Amides are not reduced directly by NaBH₄, but if they are first converted to an iminium derivative reduction to the amine is rapid. Reaction of **109** with phosphorus oxychloride (POCl₃) gave the **Vilsmeier-Haack complex**¹³⁸ (**110**), and this was reduced to the piperidine derivative **111**.¹³⁹ Primary amides are converted to nitriles by this procedure. Vilsmeier complex **110** is related to an intermediate generated in what is known as the **Vilsmeier reaction**,¹³⁸ which converts aromatic derivatives to aryl aldehydes. In a Vilsmeier reaction, POCl₃, and DMF react to form Me₂N=CHCl⁺, and this intermediate reacts with an aromatic compound to form an aldehyde after hydrolysis. Note that imides react with sodium borohydride under mild conditions to give a 2-hydroxylactam.¹⁴⁰



^{136.} Bru, C.; Thal, C.; Guillou, C. Org. Lett. 2003, 5, 1845.

^{137.} Michelliza, S.; Al-Mourabit, A.; Gateau-Olesker, A.; Marazano, C. J. Org. Chem. 2002, 67, 6474.

^{138. (}a) Vilsmeier, A.; Haack, A. Berichte 1927, 60, 119; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis 2nd Ed., Wiley, New York, 2005, pp 668-669.;(c) Witiak, D.T.; Williams, D.R.; Kakodkar, S.V.; Hite, G.; Shen, M.-S. J. Org. Chem. 1974, 39, 1242; (d) de Maheas, M.R. Bull. Soc. Chim. Fr. 1962, 1989; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-96.

^{139.} Ur-Rahman, A.; Basha, A.; Waheed, N.; Ahmed, S. Tetrahedron Lett. 1976, 219.

^{140.} For an example taken from a synthesis see Hart, D.J.; Yang, T.K. J. Chem. Soc. Chem. Commun. 1983, 135.

Anhydrides are related to lactones as imides are related to lactams. Partial reduction of an anhydride directly to an hydroxylactone is difficult, but reduction (with ring opening) to a hydroxy acid and subsequent ring closure can generate a lactone when NaBH₄ is used. An example is the reduction of anhydride **112** in DMF, to give lactone **114** in 55% yield.¹⁴¹ Norbornyl systems usually react via the exo face, as discussed in Section 1.5.E, which accounts for the selectivity of this reduction. In this particular example, reduction of the exo carbonyl gave alcohol **113**, which closed to the lactone (**114**) in the presence of the carboxyl group.



The functional group transforms for this section are

4.4.B. Alternative Metal Borohydrides (Li, Zn, Ce)

In previous sections, the metal counterion for hydride reducing agents was largely restricted to sodium, lithium or potassium. Other metals can modify the course of the reduction. Lithium borohydride (LiBH₄), for example,

NaBH₄ + LiBr → LiBH₄ + NaBr

prepared by reaction of sodium borohydride and lithium bromide,¹⁴² is a more powerful reducing agent than NaBH₄. LiBH₄ reduces aldehydes, ketones or acid chlorides as well as epoxides, esters or lactones but it does not reduce acids, nitriles or nitro compounds.¹⁴³ Lithium borohydride is soluble in ether (4 g/100 g) and THF (21 g/100 g) unlike NaBH₄, which is insoluble in the former and sparingly soluble in the latter. The major use of LiBH₄ is for the reduction of esters, when the ester is the most reducible group in the molecule. In a synthesis of citreoviral, Woerpel and Peng used LiBH₄ to reduce both the ethyl ester and the acetoxy group in **115**, to give an 87% yield of diol **116**.¹⁴⁴ Notice that reductive cleavage of the acetoxy group unmasked the alcohol unit at that carbon. Lithium borohydride usually reduces lactones to the

^{141.} Haslouin, J.; Rouessac, F. Bull. Soc. Chim. Fr. 1977, 1242.

 ⁽a) Nystrom, R.F.; Chaikin, S.W.; Brown, W.G. J. Am. Chem. Soc. 1949, 71, 3245; (b) Kollonitsch, J.; Fuchs, O.; Gábor, V. Nature 1954, 173, 125; (c) Brown, H.C.; Mead, E.J.; Subba Rao, B.C. J. Am. Chem. Soc. 1955, 77, 6209.

^{143.} Reference 15, p 603.

^{144.} Peng, Z.-H.; Woerpel, K.A. Org. Lett. 2002, 4, 2945.

corresponding diol.¹⁴⁵ Note that LiBH₄ reduces an ester in the presence of a carboxylic acid,¹⁴⁶ but there are some cases where LiBH₄ fails to reduce esters. For example, attempts to reduce the *N*-allylic pyroglutamate **117** with NaBH₄ or LiBH₄ failed.¹⁴⁷ The use of **Hojo's reagent** (lithium aluminum hydride pre-adsorbed on silica gel) solved this problem, since the reagent showed great selectivity for reduction of the most reducible group in multifunctional group molecules.^{148,149} This reagent was used to reduce **117** to the hydroxymethyl derivative (**118**) in 91% yield, without racemization of the stereogenic center at C5, in Smith and Keusenkothen's synthesis of pyrrolizidine alkaloids.¹⁴⁷ Hojo showed that silica gel is an effective catalyst for several other reactions.¹⁵⁰ Lithium borohydride is commonly used to reduce chiral oxazolidinone auxiliary to the corresponding alcohol, as in the conversion of **119** to **120** in 99% yield, in the synthesis of amphidinolide T3 by Zhao and co-workers.¹⁵¹



Metal hydrides with metal ions of higher ionic potential (such as Mg, Ca, Ba, and Sn) are also effective for the reduction of esters.^{152a,142b} Magnesium borohydride is prepared *in situ* from NaBH₄ and magnesium chloride (MgCl₂) in diglyme at 100°C, and readily reduces esters.^{150b} Addition of aluminum chloride (AlCl₃) to three equivalents of sodium borohydride generates aluminum borohydride [Al(BH₄)₃], which is a powerful reagent for the reduction lactones, epoxides, carboxylic acids, tertiary amides or nitriles as well as ketones, aldehydes or esters.¹⁵³

- 147. Keusenkothen, P.F.; Smith, M.B. Synth. Commun. 1989, 19, 2859.
- 148. Kametori, Y.; Hojo, M.; Masuda, K.; Inoue, T.; Izumi, T. Tetrahedron Lett. 1982, 23, 4585.
- 149. Kametori, Y.; Hojo, M.; Masuda, R.; Inoue, T.; Izumi, T. Tetrahedron Lett. 1983, 24, 2575.
- 150. Hojo, M. in *New Synthetic Methodology and Functionally Interesting Compounds*, Yoshida, Z. (Ed.), Kodensha-Elsevier (Tokyo/Amsterdam), **1986**, pp 43-62.
- 151. Deng, L.-S.; Huang, X.-P.; Zhao, G. J. Org. Chem. 2006, 71, 4625.
- (a) Kollonitsch, J.; Fuchs, O.; Gábor, V. *Nature (London)* 1955, 175, 346; (b) Chandrakumar, N.S.; Hajdu, J. *Tetrahedron Lett.* 1981, 22, 2949.
- 153. Brown, H.C.; Subba Rao J. Am. Chem. Soc. 1956, 78, 2582.

^{145.} For an example taken from a synthesis of the C2-C16 segment of laulimalide, see Ghosh, A.K.; Wang, Y. *Tetrahedron Lett.* 2000, 41, 2319.

^{146.} For an example taken from a synthesis of (-)-paroxetine, see Yu, M.S.; Lantos, I.; Peng, Z.-Q.; Yu, J.; Cacchio, T. *Tetrahedron Lett.* **2000**, *41*, 5647.

Zinc borohydride $[Zn(BH_4)_2]$ is prepared from zinc chloride $(ZnCl_2)$ and sodium borohydride in ether. It is most useful¹⁵⁴ for selective reduction of α , β -unsaturated aldehydes and ketones, as in the reduction of 2-cyclohexenone to 2-cyclohexenol in 96% yield (4% of cyclohexanol was formed).¹⁵⁵

Zinc borohydride is used for the diastereoselective reduction of hydroxy- or alkoxy-carbonyl derivatives (sec. 4.4.B).^{156,157} The selectivity is explained by coordination (chelation) of the zinc with the carbonyl oxygen and the proximate hydroxyl oxygen, with delivery of hydride from the less sterically hindered face of the molecule. Typical diastereoselectivity (sec. 4.7) is illustrated by formation of **122** in 77% yield (>98:2 dr) from the zinc borohydride reduction of **121**, taken from the Crimmins and co-worker's¹⁵⁸ synthesis of (–)-laulimalide.



Reduction of epoxides with high selectivity for the more substituted position, is possible using zinc borohydride supported on silica gel.^{159a} When 1-nonene oxide (2-heptyloxirane) was treated with this silica-supported reagent, an 88% yield of 1-nonanol was obtained. In general, however, epoxides can be difficult to reduce with $Zn(BH_4)_2$.^{159b} When 1-nonene oxide was treated with $Zn(BH_4)_2$ in THF, for example, only a small amount of reduction occurred to give a mixture of regioisomeric products.^{159a} Reductive cleavage of a nitrile group has also been observed when a mixture of zinc borohydride and silver tetrafluoroborate (AgBF₄) was used, as in the conversion of **123** to **124**, in Husson and co-worker's synthesis of dihydropinidine.¹⁶⁰



^{154.} Narasimhan, S.; Balakumar, R. Aldrichimica Acta 1998, 31, 19.

- (a) Nakata, T.; Fukui, M.; Ohtsuka, H.; Oishi, T. Tetrahedron Lett. 1983, 24, 2661; (b) Idem Tetrahedron 1984, 40, 2225.
- 158. Crimmins, M.T.; Stanton, M.G.; Allwein, S.P. J. Am. Chem. Soc. 2002, 124, 5958.
- (a) Ranu, B.C.; Das, A.R. J. Chem. Soc. Chem. Commun. 1990, 1334; (b) Nakata, T.; Tanaka, T.; Oishi, T. Tetrahedron Lett. 1981, 22, 4723.
- 160. Guerrier, L.; Royer, J.; Grierson, D.S.; Husson, H.-P. J. Am. Chem. Soc. 1983, 105, 7754.

^{155. (}a) Reference 124a, p 5; (b) Yoon, N.M.; Lee, H.J.; Kang, J.; Chung, J.S. Taehan Hwahak Hoechi, J. Korean Chem. Soc. 1975, 19, 468 [Chem. Abstr. 84: 134703z, 1976].

^{156.} Oishi, T. in *New Synthetic Methodology and Functionally Interesting Compounds*, Yoshida, Z. (Ed.), Kodansha-Elsevier (Tokyo/Amsterdam), **1986**, pp 81-98.

Addition of cerium salts to sodium borohydride leads to a reagent, presumably cerium borohydride (known as the Luche reagent),¹⁶¹ that gives very selective 1,2-reduction of conjugated aldehydes and ketones.¹⁶² The carbonyl of a conjugated ketone is reduced faster than that of a normal ketone. Selective 1,2-reduction was observed in the Wipf and co-worker's synthesis of (-)-tuberostemonine,¹⁶³ in which reduction of **125** gave alcohol **126** in 71% vield with high diastereoselectivity. In a generalized study, Gemal and Luche examined the extent of 1.2- versus 1.4-reduction of conjugated ketones when NaBH₄ was mixed with various metal salts.¹⁶⁴ These results are shown in Table 4.1,¹⁶⁴ and it is clear that the lanthanide salts, including cerium, show a marked preference for 1,2-reduction. Lithium and copper salts give complete reduction of both the carbonyl and the alkene mojety, whereas the other salts give mixtures of 1,2- (A) and 1,4-reduction products (B and C), although they are significantly less reactive. Addition of salts, such as Ni²⁺ or Co²⁺, give reduction of the alkene without disturbing the carbonyl, but it is possible that these reactions proceed by a completely different mechanistic pathway and large amounts of unreacted ketone often remain. The selectivity obtained when cerium salts are mixed with NaBH₄ is explained by a chelated intermediate (127). In such a complex, the carbonyl carbon coordinates the borohydride moiety and transfer of hydride to the alkene is difficult unless the complexation is reversible. If the complex is formed irreversibly, hydride transfer to the carbonyl (1.2-addition to give A in Table 4.1) is under kinetic control. If the complex forms reversibly (thermodynamic control), 1.4-reduction (to give **B** or **C** in Table 4.1) predominates.



Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, p. 805.

^{162.} Crimmins, M.T.; O'Mahoney, R. J. Org. Chem. 1989, 54, 1157.

^{163.} Wipf, P.; Rector, S.R.; Takahashi, H. J. Am. Chem. Soc. 2002, 124, 14848.

^{164.} Gemal, A.L.; Luche, J.-L. J. Am. Chem. Soc. 1981, 103, 5454.

 Table 4.1.
 1,2- vs.
 1,4-Reduction of Cyclopentenone with Sodium Borohydride Admixed with Metal Salts

\sum	$\frac{\text{NaBH}_4, \text{MeOH}}{\text{M}^+}$	H A O	\rightarrow + \rightarrow	С
<u>Metal Salt</u>	<u>% Cyclopentanone</u>	<u>% A</u>	<u>% B</u>	<u>% C</u>
La ³⁺	0	90	0	10
Ce ³⁺	0	97	0	3
Sm ³⁺	0	94	0	6
Eu ³⁺	0	93	0	7
Yb ³⁺	0	89	0	11
Y ³⁺	0	86	0	14
Li^+	0	1	0	99
Cu^+	2	6	4	88
Ba^{2+}	2	6	11	76
Zn^{2+}	90		7	3
Fe ²⁺	19	12	9	60
Fe ³⁺	33	5	12	50
Tl ³⁺	86	2	8	4
Ni ²⁺	18	0	76	6
Co ²⁺	27	0	61	12
[Reprinted with permission from Gemal, A.L.; Luche, JL. J. Am. Chem. Soc. 1981, 103, 5454. Copyright © 1981 American Chemical Society.]				

4.5. ALKOXY- AND ALKYLBOROHYDRIDES

Alkoxyborohydrides and alkylborohydrides are not used as often as metal alkoxyaluminum hydrides. In general, alkylborohydrides are more reactive than NaBH₄. Since LiAlH₄ is such a powerful regent, there is little need for alkylalumium hydrides and we will not discuss them. Alkoxyaluminates are less reactive than LiAlH₄, and alkoxyborohydrides are less reactive than NaBH₄. Acyloxy derivatives are also important. Some derivatives are unstable in ether solvents. For example, sodium trimethoxyborohydride [NaBH(OMe)₃] disproportionates in solution,¹⁶⁵ but the derivative triisopropoxyborohydride [NaBH(OiPr)₃] is very stable in THF, and is prepared in THF by treatment of B(O*i*-Pr)₃ with sodium or potassium hydride.^{165,166} This reagent¹⁶⁷ reduces only aldehydes and ketones, reacting with virtually no other functional group.

4.5.A. Acyloxyborohydrides

Acyloxyborohydrides $[NaBH_{4-n}(O_2CR)_n]$ are remarkably selective,¹⁶⁸ as illustrated by the

^{165.} Brown, H.C.; Mead, E.J.; Shoaf, C.J. J. Am. Chem. Soc. 1956, 78, 3616.

^{166.} Brown, C.A. J. Am. Chem. Soc. 1973, 95, 4100.

^{167.} Brown, C.A.; Krishnamurthy, S.; Kim, S.C. J. Chem. Soc. Chem. Commun. 1973, 391.

^{168.} Gribble, G.W.; Nutaitis, C.F. Org. Prep. Proc. Int. 1985, 17, 317.

reduction of the aldehyde unit in **128** in the presence of a ketone moiety.¹⁶⁹ Reduction with potassium triacetoxyborohydride (generated by dissolving KBH₄ in acetic acid) gave **129** in 60% yield. Good diastereoselectivity can be achieved, as in Paquette and co-worker's synthesis of (–)-sanglifehrin A.¹⁷⁰ Tetramethylammonium triacetoxyborohydride reduced the ketone unit in **130** to give **131** in 82% yield and with excellent selectivity for the diastereomer shown. In this synthesis, PMB is *p*-methoxybenzyl (see sec. 7.3.A.ii). Sodium triacetoxyborohydride has also been used for selective 1,4-reduction of conjugated esters.¹⁷¹ Acetoxyborohydride is also used for the reduction of imines and enamines, which is useful for the synthesis of alkaloid precursors. This reagent also reduces imines.¹⁷²



Reductive alkylation is possible when an amine unit is present in the substrate (sec. 4.10.D). The carbon chain of the carboxylic acid fragment is transferred to nitrogen, and an N-alkyl amine is the final product. An example is the conversion of tetrahydroquinoline (132) to the

N-propyl derivative (**133**) in 56% yield.¹⁷³ When hydroxyl groups are present in the organic substrate, acetoxylation occurs if no other reducible functional group is present. An example is the reduction



of 4-ethoxybenzyl alcohol to the *O*-acetyl derivative, in 95% yield.¹⁷⁴ Although these latter reactions can compete with the reduction of other functional groups, acyloxyborohydrides are important chemoselective reducing agents.

4.5.B. Super-Hydride™

Alkyl groups are known to be electron releasing relative to boron. Therefore, when alkyl groups are attached to the boron of a borohydride reagent the reducing power of that reagent is

^{169.} Tolstikov, G.A.; Odinokov, V.N.; Galeeva, R.I.; Bakeeva, R.S.; Akhunova, V.R. Tetrahedron Lett. 1979, 4851.

^{170.} Paquette, L.A.; Duan, M.; Konetzki, I.; Kempmann, C. J. Am. Chem. Soc. 2002, 124, 4257.

^{171.} For an example, see Hayahsi, Y.; Rohde, J.J.; Corey, E.J. J. Am. Chem. Soc. 1996, 118, 5502.

^{172.} Smith, R.G.; Lucas, R.A.; Wasley, J.W.F. J. Med. Chem. 1980, 23, 952.

^{173.} Gribble, G.W.; Heald, P.W. Synthesis 1975, 650.

^{174.} Prashad, M.; Jigajinni, V.B.; Sharma, P.N. Indian J. Chem. 1980, 19B, 822.

enhanced.^{124a,175} An extremely useful reducing agent has been developed using this idea, lithium triethylborohydride (LiBHEt₃), which is referred to as Super HydrideTM. It is prepared by reaction

BEt₃ + LiH
$$\xrightarrow{\text{THF, 65°C, 15 min}}$$
 LiBHEt₃

of lithium hydride with triethylborane in THF.¹⁷⁶ Super HydrideTM is a more powerful hydride nucleophile than LiBH₄,¹⁷⁷ giving reactions that mimic $S_N 2$ behavior. Super-HydrideTM is commonly used for the reductive dehalogenation of alkyl halides, which illustrates its nucleophilic nataure. As shown in the conversion of 2-*exo*-bromobicyclo[2.2.1]heptane (134)

to the endo-*d*-derivative (135), deuteride displacement proceeded with inversion analogous to an $S_N 2$ process.^{177,178} Sulfonate esters such as mesylates, tosylates, and triflates are reduced with LiBHEt₃ via C-O cleavage. In a synthesis of the poison-frog alkaloid (–)-205B, Smith and Kim



converted alcohol **136** to the corresponding mesylate (-CH₂OSO₂Me) and subsequent reduction with LiBHEt₃ gave reduction to the methyl group indicated in **137**, in 83% overall yield.¹⁷⁹ The reagent is highly nucleophilic, so epoxides can be opened regioselectively. Super-Hydride attacks electrophilic centers at the less sterically hindered site, as in the reduction of 1-methyl-1,2-epoxycyclohexane to 1-methyl-cyclohexanol in 99% yield.¹⁸⁰ In reactions with substrates that are sensitive to rearrangement, LiBHEt₃ is superior to LiAlH₄. Reduction of **138** with LiAlH₄ gave 15% of **139** and 85% of the rearranged alcohol **140**.¹⁸⁰ Reduction with Super-HydrideTM, however, gave 93% of **139** with < 0.1% of **140**.¹⁸⁰



Super-Hydride[™] will reduce ketones and aldehydes but it is not used extensively unless the stereochemistry of the alcohol product can be influenced by this reagent, and there are no other groups in the molecule that are reduced by this reagent. In a synthesis of (+)-panepophenathrin

^{175.} Krishnamurthy, S. Aldrichimica Acta 1974, 7, 55.

^{176.} Brown, H.C.; Krishnamurthy, S.; Hubbard, J.L. J. Am. Chem. Soc. 1978, 100, 3343.

^{177.} Brown, H.C.; Krishnamurthy, S. J. Am. Chem. Soc. 1973, 95, 1669.

^{178.} Coppi, L.; Ricci, A.; Taddei, M. J. Org. Chem. 1988, 53, 911.

^{179.} Smith, A.B., III; Kim, D.-S. Org. Lett. 2005, 7, 3247.

^{180.} Krishnamurthy, S.; Schubert, R.M.; Brown, H.C. J. Am. Chem. Soc. 1973, 95, 8486.

by Porco and co-workers,¹⁸¹ reduction of ketone **141** with lithium triethylborohydride gave a 98% yield of alcohol **142** with high diastereoselectivity, and without reduction of the epoxide unit. The model of **141** that is provided shows the relative size of the atoms and suggests that path A is more sterically hindered, leading to preferential hydride delivery along path B. Esters are reduced to alcohols, even in the presence of a lactam.¹⁸² Super-HydrideTM usually gives 1,2-reduction of conjugated carbonyl compounds,¹⁸³ and it is useful for the reduction of iminium salts. Overman and Heitz.¹⁸⁴ reported the reduction of iminium salt intermediate **144** (derived from thiolactam **143**) to the thioethyl derivative (**145**) in 84% overall yield.



4.5.C. The Selectrides

It was established in Section 4.5.B that adding alkyl groups to a borohydride unit increased the reducing power, but this strength can be modulated if the alkyl groups are sterically bulky since it is more difficult for the B–H unit to approach a substrate. The presence of large groups that provide significant steric hindrance can also lead to greater diastereoselectivity in the reduction of prochiral carbonyls. Two commonly available reagents that exploit this concept are prepared by the reaction of tri-*sec*-butylborane (147, see sec. 5.2.A for a discussion of this reagent) with potassium hydride, or lithium trimethoxyaluminum hydride to give potassium tri-*sec*-butyl-borohydride (146, known as K-SelectrideTM) or lithium tri-*sec*-butylborohydride (148, known as L-SelectrideTM).^{124a,185,166,176} Both reagents reduce aldehydes and ketones to

182. Toyooka, N.; Yoshida, Y.; Yotsui, Y.; Momose, T. J. Org. Chem. 1999, 64, 4914.

^{181.} Lei, X.; Johnson, R.P.; Porco Jr., J.A. Angew. Chem. Int. Ed. 2003, 42, 3913.

^{183.} Perron F.; Albizati, K.F. J. Org. Chem. 1989, 54, 2044.

^{184.} Heitz, M.-P.; Overman, L.E. J. Org. Chem. 1989, 54, 2591.

^{185. (}a) Brown, C.A.; Krishnamurthy, S. J. Organomet. Chem. 1978, 156, 111; (b) Binger, P.; Benedikt, G.; Rotermund, G.W.; Köster, R. J.L. Ann. Chem. 1968, 717, 21; (c) Corey, E.J.; Albonico, S.M.; Koelliker, U.; Schaaf, T.K.; Varma, R.K. J. Am. Chem. Soc. 1971, 93, 1491.

$$() \xrightarrow{BH^{-}K^{+}}_{3} \xrightarrow{KH, THF}_{25^{\circ}C} () \xrightarrow{B}_{3} \xrightarrow{\text{LiAlH}(OMe)_{3}}_{7} () \xrightarrow{BH^{-}Li^{+}}_{3}$$

$$146 \qquad 147 \qquad 148$$

the corresponding alcohol, even at temperatures as low as −78°C. Both the potassium and lithium derivatives are effective for reductions although, by analogy to other borohydrides, the lithium derivative may be somewhat stronger. In one example, L-SelectrideTM reduced the ketone moiety of **149** selectively to alcohol **150** in 80% yield as part of Weinreb and co-worker's synthesis of cylindrospermopsin.¹⁸⁶ In a synthesis of (+)-phorboxazole A,¹⁸⁷ Smith and co-workers reduced the ketone moiety in **151** with K-SelectrideTM to give alcohol **152** in 95% yield (9:1 dr). Selectride is used rather than another hydride reducing agent for its improved diastereoselectivity.



The selectivity of a SelectrideTM reagent is influenced by the addition of metal salts, just as the reactivity of NaBH₄ was modified in Section 4.4.B. Tanis and co-workers showed that **153** gave a mixture of **154** and **155** upon treatment with L-SelectrideTM and added transition metals,¹⁸⁸ via a chelated intermediate complex. Addition of magnesium bromide (MgBr₂) favored **154** (8.5:1, 95% yield) and the influence of magnesium bromide, zinc iodide (ZnI₂) and tetravalent titanium is shown in Table 4.2.¹⁸⁸ Magnesium salts gave the best results in Table 4.2, consistent with the chelating properties of that metal. Delivery of hydride from the less hindered face of **153** accounts for the preference for **154** over **155**.

Alkyl borohydrides were prepared from trisiamylborane (siamyl = $Me_2CH_2CHMe_{-}$ = trisec-isoamyl, sec. 5.2.A) with even greater steric hindrance, but with similar reactivity and selectivity to the SelectridesTM. Lithium trisiamylborohydride [LiBH(CHMeCHMe₂)] and the

^{186.} Heintzelman, G.R.; Fang, W.-K.; Keen, S.P.; Wallace, G.A.; Weinreb, S.M.J. Am. Chem. Soc. 2002, 124, 3939.

^{187.} Smith III, A.B.; Razler, T.M.; Ciavarri, J.P.; Hirose, T.; Ishikawa, T. Org. Lett. 2005, 7, 4399.

^{188.} Tanis, S.P.; Chuang, Y.-H.; Head, D.B. J. Org. Chem. 1988, 53, 4929.

potassium salt [KBH(CHMeCHMe₂)], are similar to the L- and the K-SelectridesTM and are called LS-SelectrideTM and KS-SelectrideTM, respectively.¹⁸⁹ In Ma and Zhu's synthesis of (3S,4aS,6R,8S)-hyperaspine, LS-SelectrideTM reduction of **156** gave **157** in 83% yield as a single isomer.¹⁹⁰



 Table 4.2. Influence of Metal Salts on the L-Selectride Reduction of 153

Me ^O Me ^E 153	1. MX _n 2. L-selectride HO	Me ^O Me ^e + OBn 154	HO Me IS5
<u>MX</u> n	<u>Equiv. MX_n</u>	<u> 154 : 155</u>	<u>% Yield</u>
none	0	2.8:1	99
ZnI ₂ •OEt ₂	1.5	1.1 : 1	93
$MgBr_2 \bullet OEt_2$	1.5	7.0:1	95
MgBr ₂ •OEt ₂	2.0	8.5:1	95
Ti(Oi-Pr) ₃ Cl	1.5	4.0:1	96
Ti(O <i>i</i> -Pr) ₄	1.5	5.7:1	93
[Reprinted with permission 4929. Copyright © 1988	on from Tanis, S.P.; Chuang, American Chemical Society	YH.; Head, D.B. <i>J</i> . .]	Org. Chem. 1988 , 53,

4.5.D. Sodium Cyanoborohydride

Alkyl groups are not the only substituents that can be attached to boron in order to generate new borohydride derivatives. Reaction of NaBH₄ with HCN gives sodium cyanoborohydride (NaBH₃CN),¹⁹¹ for example, a remarkably stable reagent that it is very selective,¹⁹² and does not decompose in acid solution (the pH should be less acidic than pH 3). It is soluble in THF, MeOH, H₂O, HMPA, DMF and sulfolane and they do not react.

NaBH₄ + HCN <u>THF</u> NaBH₃CN + H₂

^{189.} Krishnamurthy, S.; Brown, H.C. J. Am. Chem. Soc. 1976, 98, 3383.

^{190.} Zhu, W.; Ma, D. Org. Lett. 2003, 5, 5063.

 ^{191. (}a) Wittig, G. J.L. Ann. Chem. 1951, 573, 195 (see pp 209); (b) Wade, R.C.; Sullivan, E.A.; Berchied, Jr., J.R.; Purcell, K.F. Inorg. Chem. 1970, 9, 2146.

^{192.} Lane, C.F. Aldrichimica Acta 1975, 8, 3.

Cyanoborohydride readily reduces iodides, bromides or tosylates to the hydrocarbon in excellent yield when HMPA is the solvent,¹⁹³ even in the presence of carbonyl groups. The reduction of the iodo group in **158** gave **159** without disturbing the ester or ketone moieties for example.¹⁹⁴ Alcohols are similarly reduced if zinc bromide (ZnBr₂) is added to the reagent, as in the reduction of **160** to **161** in Johnson and co-worker's synthesis of longifolene. This reduction presumably proceeds via initial formation of a bromide, although a carbocation intermediate has also been suggested.¹⁹⁵



Ketones and aldehydes are reduced in acidic media but *not* at neutral pH. Sodium cyanoborohydride is stable at pH 3-4, where a carbonyl is converted to the protonated form $(C=OH^+)$, which is then reduced.¹⁹⁶ An example is the reduction of the aldehyde unit in **162** to give **163** in 89% yield (at pH 4 in this case), in Varela and Di Nardo's asymmetric synthesis of 4-hydroxypipecolic acid.¹⁹⁷ Note that the lactone moiety nor the benzyl carbamate were reduced under these conditions.



The ability to reduce compounds under acidic conditions is ideal for the reduction of enamines and enamides. When the reduction is done in acidic media protonation of nitrogen gives an

^{193.} Hutchins, R.O.; Milewski, C.A.; Maryanoff, B.E.. Org. Synth. Coll. Vol. 6 1988, 376.

^{194.} Hutchins, R.O.; Kandasamy, D.; Maryanoff, C.A.; Masilamani, D.; Maryanoff, B.E.J. Org. Chem. 1977, 42, 82.

^{195.} Volkmann, R.A.; Andrews, G.C.; Johnson, W.A. J. Am. Chem. Soc. 1975, 97, 4777.

^{196.} Borch, R.F.; Bernstein, M.D.; Durst, H.D. J. Am. Chem. Soc. 1971, 93, 2897.

^{197.} Di Nardo, C.; Varela, O. J. Org. Chem. **1999**, 64, 6119. For reduction of an aryl aldehyde to a mixture of a benzylic alcohol and the hydrogenolysis product in a synthesis of herbertenediol, see Srikrishna, A.; Satyanarayana, G. *Tetrahedron* **2006**, 62, 2892.

iminium salt, which is reduced *in situ* with cyanoborohydride.^{196,198} As mentioned, enamides can be reduced. In a synthesis of nominine, Muratake and co-worker's¹⁹⁹ reduced enamide **164** to the saturated derivative **165** in 91% yield using an acidic solutin of sodium cyanoborohydride. This reagent is excellent for the reduction of iminium salts at neutral pH as well,²⁰⁰ and it is also useful for the reductive alkylation of amines.²⁰¹ Dimethylamino derivatives such as **167** can be prepared from the amine (here, **166**) by treatment with formaldehyde and cyanoborohydride, even in the presence of functional groups, such as the conjugated ketone and the ester in **166**.²⁰² Apart from the actual NH₂ \rightarrow NMe₂ conversion, the selectivity for a specific group shown in this example is the major advantage in using cyanoborohydride rather than other reducing agents.



4.5.E. Typical Applications of Hydride Reducing Agents

Several hydride reducing agents were discussed in preceding sections. Knowing which reducing agent is preferred for a given situation is highly desirable, but making such a choice is not always straightforward, especially in natural product synthesis. The best reagent is the one that gives the highest yield with the fewest side reactions, but identifying this reagent often requires experimentation in the specific system being examined. Table 4.3 is presented as a simple guide to the various hydrides and their preferred use. It is very general, and should be used to only give a *first estimation* of relative reactivity.

^{198.} Hanaoka, M.; Yoshida, S.; Mukai, C. J. Chem. Soc. Chem. Commun. 1984, 1703.

^{199.} Muratake, H.; Natsume, M.; Nakai, H. Tetrahedron 2006, 62, 7093.

^{200.} Nakagawa, Y.; Stevens, R.V. J. Org. Chem. 1988, 53, 1871.

^{201.} Borch, R.F.; Hassid, A.I. J. Org. Chem. 1972, 37, 1673.

^{202.} McEvoy, F.J.; Allen, Jr., G.R. J. Med. Chem. 1974, 17, 281.

<u>Hydride</u>	Applications	Special Considerations
LiAlH ₄	General. reduces most groups: aldehydes, ketones, acids and acid derivatives, nitriles, aliphatic nitro, halides, propargyl alcohols.	Aromatic nitro reduced to diazo. Sulfonate esters give mixtures of C–O and S–O cleavage. Conjugated carbonyls often give mixtures of 1,2- and 1,4-reduction.
LiAlH(OMe) ₃	Milder than LiAlH ₄ . Generally used for aldehydes, ketones, and conversion of acid chlorides or esters to aldehydes.	Esters are reduced more slowly than ketones or aldehydes. Conjugated carbonyls give mostly 1,2-reduction. Amides and nitriles are reduced to aldehydes.
LiAlH(Ot-Bu) ₃	Mild and selective. Good for converting acid derivatives to aldehydes.	Esters are reduced more slowly than ketones or aldehydes. Conjugated carbonyls give mostly 1,2-reduction. Amides and nitriles are reduced to aldehydes.
Red-Al	Similar to LiAlH ₄ . Good for carboxylic acids. Nitriles can be converted to aldehydes and aromatic aldehydes to methyl aryls.	Conjugate carbonyls give 1,2-reduction (1,4- when Cu^+ is added). Soluble in oranic solvents, so excellent for reverse addition experiments.
NaBH ₄	General but mild. Good for ketones, aldehydes, acid chlorides, imines, iminium salts.	Esters and most acid derivatives reduce slowly, or not at all. Conjugated carbonyls give mostly 1,2-reduction, but 1,4-reduction is common. Halides are not reduced very well, but epoxides reduce very slowly
LiBH ₄	Good for esters. Stronger than NaBH ₄ ⁻ , but less selective.	Similar to NaBH ₄ , except for esters.
$Zn(BH_4)_2$	Generally similar to NaBH ₄ , but shows higher diastereoselectivity.	Similar to NaBH ₄ .
NaBH ₄ •CeCl ₃	Gives primarily 1,2-reduction with conjugated carbonyls.	Similar to NaBH ₄ .
MBH(O ₂ CR) ₃	Good for imines and enamines.	Reducing power is dependent on solvent and the nature of the R group in the RCOOH precursor. Alkylation can occur with amines, and hydroboration can occur with alkenes.
LiBHEt ₃ (Super Hydride)	Strong reducing agent. Good for halides $(S_N^2-type reductions)$, halides, and sulfonate esters (C–O cleavage).	Similar to LiAlH ₄
MBH(<i>sec</i> -Bu) ₃ (Selectride)	Used primarily with aldehydes and ketones when higher diastereoselectivity is required.	Similar to LiAlH ₄
NaBH ₃ CN	Excellent for reduction of halides at neutral pH, and alcohols if a Lewis acid is added.	Generally unreactive with most groups at neutral pH. Reduces aldehydes and ketones at pH 4 and lower. Acid derivatives are generally unreactive.

 Table 4.3. Typical reductions with selected hydride reagents

4.6. BORANE, ALUMINUM HYDRIDE, AND DERIVATIVES

4.6.A. Borane

Brown and Schlesinger first reported the preparation and use of diborane as a reducing agent in 1939.²⁰³ This finding began the exploration of hydrides and boranes as reducing agents. Borane reagents are discussed after hydrides only because hydride reagents are now used more often, but borane and its derivatives remain the reagent of choice for many applications. Diborane can be generated by reaction of $BF_3 \cdot OEt_2$ with LiH^{204} or by reaction of $NaBH_4$ and BF_3 (sec. 5.2.A).²⁰⁵

^{203.} Brown, H.C.; Schlesinger, H.I.; Burg, A.B. J. Am. Chem. Soc. 1939, 61, 673.

^{204.} Schlesinger, H.I.; Brown, H.C.; Hoekstra, H.R.; Rapp, L.R. J. Am. Chem. Soc. 1953, 75, 199.

^{205.} Zweifel, G.; Brown, H.C. Org. React. 1963, 13, 1.

$$6 \text{ LiH} + 8 \text{ BF}_3 \bullet \text{OEt}_2 \xrightarrow{\text{ether}} \text{B}_2\text{H}_6 + 6 \text{ LiBF}_4$$
$$3 \text{ NaBH}_4 + 4 \text{ BF}_3 \bullet \text{OEt}_2 \xrightarrow{\text{ether}} 2 \text{ B}_2\text{H}_6 + 3 \text{ NaBF}_4$$

Diborane (the stable dimer is B_2H_6 , but it is usually represented as BH_3 , which is an unstable monomeric form) is a potent reducing agent for aldehydes, ketones, lactones, epoxides, acids, tertiary amides and nitriles. It is ineffective for the reduction of esters, and reacts with alkenes in ether solvents, forming the basis of hydroboration chemistry (sec. 5.2). The primary difference in reactivity between borane and metal hydride reagents is that borane is a good Lewis acid and coordinates to atoms of high electron density, as illustrated by a comparison of the reduction of trichloroacetaldehyde (chloral, **168**) to give the alcohol (**169**), and similar reduction of 2,2-dimethylpropanal (pivalaldehyde, **170**) to give **171**. Sodium borohydride reduced **168** faster than **170**. Diborane, however, reacted faster with **170** due to the more electron-rich carbonyl oxygen.²⁰⁶



As mentioned above, borane reduces esters very slowly, and ketones or aldehydes are selectively reduced in the presence of esters. The most widely used application of borane, however, is for the selective reduction of carboxylic acids even in the presence of halides, esters, nitriles or ketones.²⁰⁷ The dimethyl sulfide•borane complex is commercially available and is often the reagent of choice for this reduction. Although LiAlH₄ reduces both acids and esters and NaBH₄ does not reduce acids (and often reduces esters with difficulty), borane selectively reduces carboxylic acids in the presence of an ester group. Reduction occurs without racemization of adjacent chiral centers, as in the borane reduction of (–)-malic acid to generate (*S*)-1,2,4-butanetriol in 92% yield.²⁰⁸ A typical synthetic application is taken from a synthesis of (+)-SCH 351448,²⁰⁹ in which Lee and co-workers reduced the carboxylic acid unit in **172** to give alcohol **173** using borane-dimethyl sulfide. Borane also reduces epoxides at the less hindered carbon when mixed with catalytic amounts of sodium borohydride.²¹⁰ Borane is useful for the conversion of α-amino acids to α-amino alcohols, as in the reduction of phenylalanine to phenylalaninol in 77% yield.²¹¹ Lactams are also reduced to cyclic amines.²¹²

^{206.} Reference 124a, p 7.

^{207.} Boger, D.L.; Yohannes, D. J. Org. Chem. 1989, 54, 2498.

 ^{208. (}a) Hanessian, S.; Ugolini, A.; Therien, M. J. Org. Chem. 1983, 48, 4427; (b) Nakata, T.; Nagao, S.; Oishi, T. Tetrahedron Lett. 1985, 26, 75.

^{209.} Kang, E.J.; Cho, E.J.; Lee, Y.E.; Ji, M.K.; Shin, D.M.; Chung, Y.K.; Lee, E. J. Am. Chem. Soc. 2004, 126, 2680.

^{210.} Klunder, J.M.; Onami, T.; Sharpless, K.B. J. Org. Chem. 1989, 54, 1295.

^{211. (}a) Lane, C.F. U.S. Patent 3,935 280 1976 [Chem. Abstr. 84: 135101p 1976]; (b) Reference 30a, p 54.

^{212.} For a synthetic example taken from a synthesis of balanol, see Lampe, J.W.; Hughes, P.F.; Biggers, C.K.; Smith, S.H.; Hu, H. J. Org. Chem. 1996, 61, 4572.

$$Me_{3}SiH_{2}CH_{2}CO_{2}C$$

$$Me_{3}SiH_{2}C$$

The flammability and difficulties²¹³ in handling gaseous borane led to development of several stable Lewis base complexes that are easier to use. As noted in the reduction of **172**, one of the more useful reagents is the borane complex of DMS ($H_3B \cdot SMe_2$) where DMS is dimethylsulfide, prepared by bubbling DMS into a THF solution of diborane. This reagent is very soluble in most organic solvents, including benzene and toluene, and gives all the selectivity expected for borane.²¹³

Otherboranessuchasbis(1,2-dimethylpropyl)borane(disiamylborane),and9-borabicyclo[3.3.1] nonane (usually referred to as simply 9-BBN), both discussed in section 5.2.A, reduce organic functional groups in a manner similar to borane.²¹⁴ There are interesting differences in selectivity. Dialkylboranes reduce esters and lactones, whereas similar reduction with borane is very slow. Dicyclohexylborane, for example, reacted with **174** to give 4-deoxyerythropentose (**175**).²¹⁵ Tertiary amides are reduced by dialkylboranes to the corresponding aldehyde.^{214a} An example is the reduction of *N*,*N*-dimethylbenzamide with disiamylborane to give benzaldehyde in 89% yield.^{214a} The increased steric hindrance of the reagent can have a significant effect on the selectivity in the reduction of prochiral ketones, relative to reduction with LiAlH₄ or NaBH₄.



4.6.B. Aluminum Hydride

Borane (BH₃) is considered to be a Lewis acid when compared with borohydride (BH₄⁻), which is an *ate* complex of borane. Similarly, AlH_4^- has an electrophilic analog, aluminum hydride (AlH₃), and is capable of selective reduction for many organic functional groups, and is usually prepared by reaction of three equivalents of LiAlH₄ with aluminum chloride (AlCl₃).²¹⁶

 $3 \text{ LiAlH}_4 + \text{ AlCl}_3 \longrightarrow 4 \text{ AlH}_3 + 3 \text{ LiCl}$

^{213.} Lane, C.F. Aldrichimica Acta 1975, 8, 20.

^{214. (}a) Brown, H.C.; Bigley, D.B.; Arora, S.K.; Yoon, N.M. J. Am. Chem. Soc. 1970, 92, 7161; (b) Brown, H.C.; Krishnamurthy, S.; Yoon, N.M. J. Org. Chem. 1976, 41, 1778.

^{215.} Nakaminami, G.; Shoi, S.; Sugiyama, Y.; Isemura, S.; Shibuya, M.; Nakagawa, M. *Bull* Chem. *Soc. Jpn. 1972*, *45*, 2624.

 ⁽a) Eliel, E.L. Rec. Chem. Progr., 1961, 23, 129; (b) Doukas, H.M.; Fontaine, T.D. J. Am. Chem. Soc. 1951, 73, 5917; (c) Idem, Ibid. 1953, 75, 5355; (d) Wiberg, E.; Schmidt, M. Z. Naturforsch. 1951, 6B, 333, 460.

Aluminum hydride prepared in this way is not always pristine since mixed chloroaluminum hydrides can be formed, depending on the proportions of lithium aluminum hydride and aluminum chloride.²¹⁷ The most common mixed hydrides are Cl₂AlH and ClAlH₂, and adjusting the stoichiometry of the reagents can produce either as the major product. When properly prepared, aluminum hydride reduces aldehydes, ketones, acid chlorides, epoxides, acids, tertiary amides or nitriles with ease. Its most common use, however, is the selective 1,2-reduction of conjugated aldehydes, ketones or esters, as in the reduction of the conjugated ester in **176** to the allylic alcohol moiety in **177** (94% yield) in Wilson and Zucker's synthesis of the melon fly pheromone.²¹⁸ Similar selectivity is observed with conjugated ketones as shown by the AlH₃ reduction of 2-cyclopentenone to cyclopentenol (**178**, 90% yield), with cyclopentanol as a minor product.²¹⁹ It is sometimes possible to control the 1,2- versus 1,4-selectivity of LiAlH₄, however, by changing reaction conditions. Reduction of cyclopentenone with LiAlH₄ in diethyl ether at -70°C gave an 85% yield of cyclopentenol.²¹⁹





The preference for 1,2-reduction is explained by the Lewis acidity of AlH₃. Initial complexation of aluminum hydride with the carbonyl (as in **179**) makes it difficult for the hydride to be delivered to the alkene moiety via a six-center transition state. The four-center transition state required for delivery of hydride to the carbonyl carbon is, by comparison, very easy to attain. If the complexation is strong, as with

AlH₃, then 1,2-reduction predominates. When the coordination is relatively weak, as with LiAlH₄, both 1,2- and 1,4-reduction are observed. Aluminum hydride reduces other functional groups as well. In the synthesis of a new phenanthro[9,10,3',4']indolizidine by Wang and co-workers,^{220a} lactam **180** was reduced to amine **181** in 80% yield using a mixture of LiAlH₄/AlCl₃. In a synthesis of bis(benzofuran) cations with antiprotozoal activity by Tidwell and co-workers, bis(benzofuran-2-yl) ketones were reduced with LiAlH₄/AlCl₃ to the corresponding bis(benzofuran-2-yl)methane.^{220b}

^{217.} Diner, U.E.; Davies, H.A.; Brown, R.K. Can. J. Chem. 1967, 45, 207.

^{218.} Wilson, S.R.; Zucker, P.A. J. Org. Chem. 1988, 53, 4682.

^{219.} Brown, H.C.; Hess, H.M. J. Org. Chem. 1969, 34, 2206.

^{220. (}a) Wang, K.; Wang, Q.; Huang, R. J. Org. Chem. 2007, 72, 8416; (b) Bakunova, S.M.; Bakunov, S.A.; Wenzler, T.; Barszcz, T.; Werbovetz, K.A.; Brun, R.; Hall, J.E.; Tidwell, R.R. J. Med. Chem. 2007, 50, 5807.



4.6.C. Diisobutylaluminum Hydride

It is often difficult to generate pure AlH₃, which may cause problems in reactions with sensitive substrates. Alkylalanes have been developed that are analogous to the alkylboranes, and these have proven to be quite useful. A commercially available and commonly used alkyl derivative is diisobutylaluminum hydride ([(CH₃)₂CHCH₂]₂AlH, **Dibal** or Dibal-H), prepared by refluxing triisobutylaluminum in the solvent heptane, although other solvents can also be used.²²¹ It is a pyrophoric liquid when used neat, so it is commonly used as a heptane or ether solution. Dibal-H is a strong reducing reagent, reducing most functional groups but the synthetic utility lies in three areas: reduction of esters, reduction of lactones, and reduction of nitriles. Esters are commonly reduced to the alcohol analogous to LiAlH₄, as illustrated by reduction of the ester unit in **182** to the hydroxymethyl group in **183** in 86% yield, in Trost and co-worker's synthesis of marcfortine B.²²² Note that the lactam moieties are not reduced under these conditions, and PMB is *para*-methoxybenzyl. Another quite useful reduction of **184** to **185**, taken from Leahy and co-worker's synthesis of rhizoxin D.²²³



223. Lafontaine, J.A.; Provencal, D.P.; Gardelli, C.; Leahy, J.W. J. Org. Chem. 2003, 68, 4215.

 ⁽a) Ziegler, K.; Geller, H.G.; Lehmkuhl, H.; Pfohl, W.; Zosel, K. Annalen, 1960, 629, 1; (b) Reference 15, p 260; (c) Eisch, J.J.; Kaska, W.C. J. Am. Chem. Soc. 1966, 88, 2213; (d) Gensler, W.J.; Bruno, J.J. J. Org. Chem. 1963, 28, 1254.

^{222.} Trost, B.M.; Cramer, N.; Bernsmann, H. J. Am. Chem. Soc. 2007, 129, 3086.



In some cases, it is possible to limit the reduction to give an aldehyde.²²⁴ Generally, reduction of an ester at low temperature leads to the aldehyde whereas reduction at higher temperatures leads to the alcohol. An example is the reduction of the ester unit in **186** in toluene at -78° C to give aldehyde **187** in 93% yield as part of the Dias and Meira synthesis of the C11-C11 fragment of callystatin A.²²⁵ In that same work, but later in the synthesis conjugated ester **188** was reduced to alcohol **189** with Dibal-H in dichloromethane at 0°C (in 95% yield). Clearly, both the solvent and the temperature plays a role in this reduction. In many cases, however, significant amounts of alcohol are formed even at low temperatures.



Dibal-H is also used for the reduction of lactones to lactols, which are not always stable. In a synthesis of crispatenine by Parrain and co-workers,²²⁶ lactone **190** was reduced to lactol **191** in 95% yield with Dibal.



When mixed with alkylcopper reagents (MeCu or *t*-BuCu are the most common), Dibal-H gives selective 1,4-reduction of conjugated carbonyl compounds. An example, taken from Corey and Huang's synthesis of desogestrel, is the conversion of **192** to **193** in 91% yield using HMPA as a solvent.²²⁷ Dibal-H also reduces nitriles to aldehydes. A synthetic example, taken from Andrus' and co-worker's synthesis of (+)-geldanamycin,²²⁸ treated nitrile **194** with Dibal-H and then water to give a 92% yield of **195**.

^{224. (}a) Boger, J.; Payne, L.S.; Perlow, D.S.; Lohr, N.S.; Poe, M.; Blaine, E.H.; Ulm, E.H.; Schorn, T.W.; LaMont, B.I.; Lin, T.-Y.; Kawai, M.; Rich, D.H.; Veber, D.H. *J. Med. Chem.* **1985**, 28, 1779; (b) Luly, J.R.; Hsiao, C.-N.; BaMaung, N.; Plattner, J.J. *J. Org. Chem.* **1988**, 53, 6109.

^{225.} Dias, L.C.; Meira, P.R.R. Tetrahedron Lett. 2002, 43, 8883.

^{226.} Bourdron, J.; Commeiras, L.; Audran, G.; Vanthuyne, N.; Hubaud, J.C.; Parrain, J.-L. *J. Org. Chem.* 2007, 72, 3770.

^{227.} Corey, E.J.; Huang, A.X. J. Am. Chem. Soc. 1999, 121, 710.

^{228.} Andrus, M.B.; Meredith, E.L.; Hicken, E.J.; Simmons, B.L.; Glancey, R.R.; Ma, W.J. Org. Chem. 2003, 68, 8162.



It is clear that borane and aluminum hydride, along with their alkyl derivatives, offer significant advantages for the reduction of many functional groups. Borane is often the reagent of choice for reduction of acids in the presence of esters, aluminum hydride for selective 1,2-reduction of conjugated carbonyls, and Dibal-H for partial reduction of lactones and conversion of esters and nitriles to aldehydes. It should be pointed out that Dibal-H also reduces ketones and aldehydes. Reduction of chiral ketone **196** in Table 4.4,²²⁹ which has a methoxy group α - to the carbonyl that is subject to hydrogenolysis, was reduced to a 99:1 mixture of the *anti*-alcohol (**197**) and the *syn*-alcohol (**198**).²²⁹ This example was included to raise a specific question. Why is Dibal-H so selective that **197** is formed as the major product (why is it so diastereoselective)? That question is addressed in Section 4.7.

Ph Ph H OMe	Dibal-H, –78°C HO HO HO H	$\begin{array}{c} H \\ Ph \\ OMe \end{array} + \begin{array}{c} H \\ Ph \\ H \end{array}$	OH Ph OMe
196	19	1 97 19	98
Reducing Agent	Conditions	% Yield	<u> 197 : 198</u>
LiAlH ₄	THF, 0°C, 5h THF, –78°C, 1h THF-HMPA, 0°C, 5h	89 85 82	93.5 : 6.5 95 : 5 90.4 : 9.6
Dibal-H	ether, -78° C, 1h toluene, -78° C, 2.5h THF, -78° C, 1h	84 83 78 85	97:3 98:2 87:13 99:1
KBH_4	MeOH (aq), 0°C, 0.5h 86 90 : 10		90:10
K-Selectride	THF, -78°C, 1h ether, -78°C, 3h	79 68	98:2 98:2
PhSiMe ₂ H, Bu ₄ NF H ₂ /Pd	HMPA, 25°C, 32h EtOH, 25°C, 5h	0 98	76 : 24
[Reprinted with permission from Davis, F.A.; Serajul Haque, M.; Przeslawski, R.M. J. Org. Chem. 1989, 54, 2021 Copyright © 1989 American Chemical Society.]			

Table 4.4. Diastereoselectivity with Different Reducing Agents for the Reduction of 196

4.7. STEREOSELECTIVITY IN REDUCTIONS

Hydride reduction of prochiral ketones generally gives alcohol products with good diastereoselectivity, but each diastereomer is racemic. An example is the reduction of **196** with

^{229.} Davis, F.A.; Haque, M.S.; Prezeslawski, R.M. J. Org. Chem. 1989, 54, 2021.

various reducing agents shown in Table 4.4,^{230a} where it is clear that the diastereoselectivity (anti/syn selectivity) for reduction of such substrates depends on the reducing agent as well as the reaction conditions. When diastereomers are formed by reduction of carbonyl groups, is it possible to predict the relative stereochemistry of such reductions and also the absolute stereochemistry? The following sections will attempt to answer these questions.

4.7.A. Chiral Additives in Acyclic Systems

The stereochemistry of a product is an important consideration when a functional groups is reduced, as seen in Table 4.4. When 2-pentanone is reduced to 2-pentanol, for example, the carbonyl is a prochiral center (sec. 1.4.E) since addition of hydride from either of the two faces (a or b) of the carbonyl unit in 2-pentanone will generate the two enantiomers of 2-pentanol.^{230b} Both faces are equally susceptible to attack, so the alcohol product is racemic and most hydride reagents discussed previously will generate racemic products. Acyclic ketones or aldehydes without a pendant chiral center will also give racemic alcohols. Enantioselectivity is not possible with the simple reagents presented so far, but the use of a chiral reducing agent is expected to give enantioselective reductions.

If a stereogenic center is present in the molecule, reduction will generate diastereomers. Delivery of hydride to the carbonyl unit in **199** can be from both the re and si faces. The presence of the (R)-stereocenter adjacent to the carbonyl, however, means that reduction from the re face gives one diastereomer (**200**) and delivery from the si face gives the other diastereomer (**201**). In some cases, the stereocenter in the ketone can influence the stereochemistry of the newly formed hydroxyl group in the alcohol product. Reductions of this type will be discussed in section 4.7.B.



Development of chiral reducing agents led to enantioselective reductions. Morrison and Mosher described this approach in a monograph that covered the literature up to approximately

^{230. (}a) Harding, K.E.; Strickland, J.B.; Pommerville, J. J. Org. Chem. **1988**, 53, 4877; (b) For reagents that lead to asymmetric reduction of aldehydes or ketones, see Reference 17, p 1097.



1970.²³¹ Early work prepared chiral reagents by reacting hydride reagents with natural products that contained stereogenic centers of known absolute stereochemistry, such as (–)-camphor (**202**)^{232,233} or (–)-menthol (**203**).^{233b} Reaction of these molecules with LiAlH₄ prior to addition of a substrate with a prochiral carbonyl led to a reagent capable of reducing the carbonyl with modest asymmetric induction.

These reagents were not very effective, however. Reduction of methyl *tert*-butyl ketone (3,3-dimethyl-2-butanone), for example, showed no asymmetric induction when the product (3,3-dimethyl-2-butanol) was analyzed. Other chiral natural products have been attached to LiAlH₄, leading to reductions that proceed with moderate-to-good enantioselectivity. Quinine reacted with LiAlH₄ to give **204**, whereas (+)-(*2S*,*2R*)-1,2-diphenyl-3-methyl-4-dimethylamino-2-butanol (Darvon alcohol; Darvon is the O₂CEt ester of this alcohol) gave **205**, and ephedrine gave **206**. The lithium aluminum hydride products of both (+)-quinidine (**207**, a diastereomer of quinine) and (+)-cinchonine (the derivative of quinidine without the OMe group on the quinoline unit) are chiral reducing agents.²³¹ *Cinchona* alkaloids such as these were used by Sharpless as chiral additives in the **Sharpless asymmetric dihydroxylation** reaction, which was discussed in Section 3.5.B.ii. Acetophenone reacted with **204**, for example, to give the alcohol with 45% ee, but **206** gave only 13% ee (*R*)-and **207** 23% ee (*S*).²²⁴



Lithium aluminum hydride derivatives of monosaccharides reduce some ketones with moderate % ee. The bis(alkoxy) derivative of LiAlH₄-3-*O*-benzyl-1,2-cyclohexylidene α -*D*-glucofuranose (**208**), and the analogous 1:1 ethanol adduct (**209**) are examples.²³⁵ Reducing agent **208** reacted with acetophenone to give (*S*)-phenethyl alcohol in 33% ee. Adduct **209** showed greatly improved but opposite selectivity, giving 71% ee in the product (*R*)-phenethyl alcohol when reacted with acetophenone.

234. Reference 231, p 205 and citations 75 and 74, 76-80 cited therein.

^{231.} Morrison, J.D.; Mosher, H.S. *Asymmetric Organic Reactions*, American Chemical Society, Washington, DC 1976, pp. 202-218.

^{232.} Bothner-By, A.A. J. Am. Chem. Soc. 1951, 73, 846.

 ⁽a) Portoghese, P.S. J. Org. Chem. 1962, 27, 3359; (b) Landor, S.R.; Miller, B.J.; Tatchell, A.R. Proc. Chem. Soc. 1964, 227; (c) Idem J. Chem. Soc. C 1966, 1822.

 ⁽a) Reference 231, p 214; (b) Landor, S.R.; Tatchell, A.R. J. Chem. Soc. C 1966, 2280; (c) Landor, S.R.; Miller, B.J.; Tatchell, A.R. Ibid. 1967, 197.



The structural features that lead to asymmetric induction vary with the reagent, making generalization difficult. Landor found that H_b in **208**, for example, was transferred to a carbonyl group during reduction faster than H_a . Acetophenone was reduced to give the (*S*)-alcohol, and this demands that the ketone approach H_b in **208** away from the protruding *O*-benzyl group as shown. This model corresponds to approach of the reagent from the *re* face. Presumably, the methyl-oxygen lone-pair interaction is less than the phenyl-oxygen lone pair interaction. This difference is not great and the observed enantioselectivity was only modest. The 3D models of both **208** and **209** are provided, with an acetophenone molecule approaching from the face indicated in the 2D model. When ethanol was incorporated into the reagent (see **209**), H_b was replaced with an ethoxy group so H_a was the only source of hydride. The carbonyl must now approach on the same face of the carbohydrate as before, but to reduce steric interactions the orientation of the ketone relative to H_a places the larger phenyl group up and away from the sugar moiety (the *si* face). This approach leads to reduction that generates the (*R*)-alcohol.²³⁵

This steric analysis is attractive, does not apply to reagents such as the LiAlH₄-Darvon alcohol reagent (see **205**), prepared by Mosher (Darvon alcohol is **210**).²³⁶ First of all, the hydride reacts to form an alkoxyaluminate (**207**) where the value of *n* may be 1, 2, or 3 (although *n* was shown to be 1 in **211** and is probably 2 after the initial reaction of LiAlH₄ with **210**). Second, the coordination state of the aluminum is unknown (both tetrahedral and octahedral coordination complexes are possible). Finally, the age of the reagent is important. Freshly prepared **211** is insoluble in ether solvents and reacts selectively to give the (*R*)-phenethyl alcohol from acetophenone. If the reagent is allowed to age, it becomes soluble and gives the (*S*)-alcohol when used for reduction, but this is probably not due to formation of a tris(alkoxy)aluminate (*n* = 3). These ambiguities preclude the simple steric analysis that was possible with the structurally

^{236. (}a) Yamaguchi, S.; Mosher, H.S. J. Org. Chem. 1973, 38, 1870; (b) Yamaguchi, S.; Mosher, H.S.; Pohland, A. J. Am. Chem. Soc. 1972, 94, 9254.

well-defined **208** and **209**. When the structure of the active reducing agent is known, steric and facial arguments can predict approach to the carbonyl from the less hindered face with an orientation that minimizes steric interactions (generating the major diastereomer or enantiomer).

Ph Ph
$$210$$
 H NMe₂ LiAlH₄
R* indicates a chiral group LiAlH_{4-n}(OR*)_n
211

Borane was shown to be a potent reducing agent in section 4.6.A and chiral boranes function as reducing agents for carbonyl compounds.²³⁷ Brown prepared a variety of chiral boranes in connection with extensive studies of hydroboration reactions (sec. 5.4.B). Reaction of diborane and α -pinene gave (–)-(1*R*,2*S*,3*R*,5*R*)-diisopinocampheylborane (**212**), and this chiral borane



reduced carbonyl derivatives to alcohols with high asymmetric induction.²³⁸ Trialkylboranes are also capable of reducing carbonyls, but by a different mechanism (i.e. hydride comes from C–H rather than Al–H or B–H). Boranes such as the (–)-(1*R*,2*S*,3*S*,5*S*) complex between pinene and 9-BBN [**213** (R' = H), B-3-pinanyl-9-borabicyclo-[3.3.1]nonane = Alpine borane[®]] are chiral²³⁹ and were used by Midland and co-workers for the asymmetric reduction of aldehydes and ketones. Alpine borane[®] reduced *d*-butanal to *d*₁-1-butanol with high enantioselectivity.²⁴⁰ The source of hydride in Alpine borane[®] (and generally in trialkylboranes) is the tertiary hydrogen (R' = H) that has been replaced by deuterium in **213** (R' = *d*). Reduction of butanal gave the *(R)*-deuterobutanol (**211**, where R' = *d*) and pinene (**214**).²³¹ The first important consideration is the observation that tertiary β-hydrogens in these boranes are removed much faster than the secondary or primary β-hydrogens.^{241,239a} Approach of the carbonyl to this hydrogen must occur from the face (**216**) that is nearest to the tertiary β-hydrogen (R' = D in **217**). It might



- 237. For a discussion of factors controlling stereoselectivity in such reductions, see Rogic, M.M. J. Org. Chem. 2000, 65, 6868.
- 238. (a) Brown, H.C.; Zweifel, G. J. Am. Chem. Soc. 1961, 83, 486; (b) Brown, H.C.; Bigley, D.B. Ibid. 1961, 83, 3166.
- (a) Midland, M.M.; Tramontano, A.; Zderic, S.A. J. Organomet. Chem. 1978, 156, 203; (b) Midland, M.M.; Tramontano, A.; Zderic, S.A. J. Am. Chem. Soc. 1977, 99, 5211.
- 240. (a) Midland, M.M.; Greer, S.; Tramontano, A.; Zdevic, S.A. J. Am. Chem. Soc. 1979, 101, 2352; (b) Midland, M.M. McDowell, D.C.; Hatch, R.L.; Tramontano, A. J. Am. Chem. Soc. 1980, 102, 867.
- 241. Midland, M.M.; Tramonatano, A.; Zderic, S.A. J. Organomet. Chem. 1977, 134, C17.

appear at first that the R= group in the aldehyde (R = *n*-propyl) would prefer to be oriented away from the pinanyl ring, but in fact the opposite is true. Examination of **216** shows the R group is over the pinanyl ring but away from the protruding bridgehead hydrogen, which is the required approach for reduction (the *re* face of the aldehyde) and there is minimal steric interaction.²⁴⁰ When the aldehyde approaches with the opposite orientation (the *si* face as in **217**) the R group interacts with the hydrogens on the methyl group, sterically destabilizing **217**.²⁴⁰ The orientation in **216** is preferred, leading to the (*R*)-alcohol in this case. The extent of selectivity observed in the reduction of ketones depends on the relative size and nature of the groups attached to the carbonyl. An example is taken from a synthesis of (–)-archazolid B²⁴² by Trauner and co-workers, in which propargylic ketone **218** was reduced to alcohol **219** in 89% yield (>20:1 dr).

$$t-BuMe_2SiO \underbrace{\xrightarrow{\overline{1}}}_{218} \underbrace{(S)-Alpine \text{ borane}}_{THF, 40^{\circ}C} \underbrace{t-BuMe_2SiO}_{219} \underbrace{\xrightarrow{Me}}_{OH}$$

The asymmetric reduction of ketones by borane is catalyzed by chiral oxazaborolidines,²⁴³ and is widely used for the preparation of chiral secondary alcohols.²⁴⁴ The factors that influence enantioselectivity of the asymmetric reduction have been described,²⁴⁵ as have the influence of electronic effects and anions on the enantioselectivity of such reductions.²⁴⁶ In a synthesis of (+)-cryptophycin 52,²⁴⁷ a potent antimitotic antitumor agent, Ghosh and Swanson reduced keto ester **220** with borane using a catalytic amount of oxazaborolidine **221**, which had been previously prepared by Corey.²⁴⁸ The chiral alcohol product **222**, formed initially, cyclized via an intramolecular transesterification to lactone **223** in 84% yield and 97% optical purity.

$$\begin{array}{c} O \\ Ph \\ Ph \\ 220 \end{array} \xrightarrow{O \\ H \\ H \\ 220 \end{array} \xrightarrow{Ph \\ H \\ H \\ 221 \\ Me \\ Ph \\ 221 \\ Me \\ Ph \\ 221 \\ Me \\ Ph \\ 222 \\ Ph \\ 223 \\ Ph \\$$

With all reagents generated by addition of chiral materials to LiAlH₄, their exact structure

- 246. Xu, J.; Wei, T.; Zhang, Q. J. Org. Chem. 2004, 69, 6860.
- 247. Ghosh, A.K.; Swanson, L. J. Org. Chem. 2003, 68, 9823.
- 248. Corey, E.J.; Bakshi, R.K.; Shibata, S.; Chen, C.; Singh, V.K. J. Am. Chem. Soc. 1987, 109, 7925.

^{242.} Roethle, P.A.; Chen, I.T.; Trauner, D. J. Am. Chem. Soc. 2007, 129, 8960

^{243.} Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakashama, S. Bull. Chem. Soc. Jpn. 1987, 60, 395.

^{244. (}a) Corey, E.J.; Helal, C.J. Angew. Chem. Int. Ed., 1998, 37, 1986; (b) Deloux, L.; Srebnik, M. Chem. Rev. 1993, 93, 763; (c) Singh, V.K. Synthesis 1992, 605; (d) Wallbaum, S.; Martens, J. Tetrahedron: Asymmetry 1992, 3, 1475.

^{245. (}a) Corey, E.J.; Bakshi, R.K.; Shibata, S. J. Am. Chem. Soc. 1987, 109, 5551; (b) Corey, E.J.; Link, J.O. *Tetrahedron Lett.* 1989, 30, 6275; (c) Puigjaner, C.; Vidal-Ferran, A.; Moyano, A.; Pericas, M.A.; Riera, A. J. Org. Chem. 1999, 64, 7902; (d) Gilmore, N.J.; Jones, S. *Tetrahedron: Asymmetry* 2003, 14, 2115; (e) Xu, J.X.; Wei, T.Z.; Zhang, Q.H. J. Org. Chem. 2003, 68, 10146.

must be determined before facial and orientation preferences can be determined for a given substrate. As illustrated by Alpine borane[®], the mechanism of hydride transfer must also be known. When these parameters are known, careful examination of models (Dreiding[®] models or computer generated modeling) should determine the actual steric interactions. Casual inspection of a line drawing is usually insufficient for accurate predictions.

Morrison and Mosher collected data for asymmetric induction in the reduction of several acyclic ketones and their monograph is an excellent source when one must choose an asymmetric reducing agent.²⁴⁹ The use of (–)-**212** for reduction of acetophenone in diglyme, for example, gave 14% ee [(*R*)-phenethyl alcohol]. Similar reduction of ethyl isopropyl ketone (2-methyl-3-propanone) gave 62% ee of the (*S*)-alcohol in THF.²⁴⁹ Many reagents have been developed and used in organic synthesis. Brown compared several chiral boranes with other chiral complexes for the reduction of several cyclic and acyclic ketones.²⁵⁰ Other chiral reagents used for reduction include enantrane (**224**),²⁵¹ diisopinylcamphenyl chloroborane (Ipc₂BCl, **225**),²⁵² the mixture of diborane and AMDPB (**226**),²⁵³ (2*R*,5*R*)-dimethylborolane (**227**),²⁵⁴



NB-enantride (**228**),²⁵⁵ (*S*,*S'*)-*N*,*N'*-dibenzoylcystine and (**229**) and lithium borohydride,²⁵⁶ 1,2,5,6-di-*O*-isopropylidene-*D*-glucofuranose (**230**) and sodium borohydride,²⁵⁷ K-glucoride (**231**),²⁵⁸ a mixture of LiAlH₄ and *N*-methylephedrine (**232**) in the presence of

^{249.} Reference 231, p 216 and citations 84-87 therein.

^{250.} Brown, H.C.; Park, W.S.; Cho, B.T.; Ramachandran, P.V. J. Org. Chem. 1987, 52, 5406 and references cited therein.

^{251.} Midland, M.M.; Kazubski, A. J. Org. Chem. 1982, 47, 2814.

^{252. (}a) Chandrasekharan, J.; Ramachandran, P.V.; Brown, H.C. J. Org. Chem. 1985, 50, 5446; (b) Brown, H.C.; Chandrasekharan, J.; Ramachandran, P.V. Ibid. 1986, 51, 3394. For a review, see (c) Ramachandran, P.V.; Brown, H.C. in *Reductions in Organic Synthesis. Recent Advances and Practical Applications*, Abdel-Magid, A.F (Ed.), ACS Symposium Series 641, American Chemical Society, Washington, D.C., 1996. pp 84-97

⁽a) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. J. Chem. Soc. Perkin Trans. 1, 1985, 2039; (b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. J. Org. Chem. 1984, 49, 555; (c) Hirao, A.; Itsuno, S.; Nakahama, S.; Yamazaki, N. J. Chem. Soc. Chem. Commun. 1981, 315.

^{254.} Imai, T.; Tamura, T.; Yamamuro, A.; Sato, T.; Wollmann, T.A.; Kennedy, R.M.; Masamune, S. J. Am. Chem. Soc. 1986, 108, 7402.

^{255.} Midland, M.M.; Kazubski, A. J. Org. Chem. 1982, 47, 2495.

 ⁽a) Soai, K.; Oyamada, H.; Yamanoi, T. J. Chem. Soc. Chem. Commun. 1984, 413; (b) Soai, K.; Yamanoi, T.; Hikima, H.; Oyamada, H. Ibid. 1985, 138.

^{257. (}a) Hirao, A.; Nakahama, H.; Mochizuki, D.; Itsuno, S.; Ohowa, M.; Yamazaki, N. J. Chem. Soc. Chem. Commun. 1979, 807; (b) see Morrison, J.D.; Grandbois, E.R.; Howard, S.I. J. Org. Chem. 1980, 45, 4229.

^{258.} Brown, H.C.; Park, W.S.; Cho, B.T. J. Org. Chem. 1986, 51, 1934, 3278, 3396.

3,5-dimethylphenol,²⁵⁹ a mixture of LiAlH₄ and (*S*)-2-(2,6-xylidinomethyl)-pyrrolidine (**236**),²⁶⁰ the lithium aluminum hydride-(*S*)-(4-anilino)-3-(methylamino)-1-butanol complex (**233**),²⁶¹ Binal-H (**235**),²⁶² the lithium aluminum hydride-ethanol-(*S*)-(–)-10,10'-dihydroxy-9,9'-biphenanthryl complex (**234**),²⁶³ the lithium aluminum hydride-**232**-*N*-ethylaniline complex,²⁶⁴ the lithium aluminum hydride-**232**-2-(ethylamino)-pyridine complex,²⁶⁵ and an enzymatic reduction (sec. 4.10.F) with *Thermoanaerobium brockii* alcohol dehydrogenase (**237**).²⁶⁶ Brown and co-workers collected these data into Table 4.5,²⁵⁰ to identify the preferred chiral reducing agents for different classes of ketones. Table 4.5 provides general data and it is not exhaustive, but the term effectiveness presumably refers to the order in which the reagents appear. The reagent giving the highest % ee with good yields of the reduction products appears at the top of the list with the following reagents being less effective. This table allows one to choose a chiral additive and reducing agent for reduction of a given type of ketone. Brown also described a series of chiral boronic ester *ate* complexes that showed high diastereoselectivity for the reduction of ketones.²⁶⁷



 ⁽a) Vigneron J.-P.; Bloy, V. *Tetrahedron Lett.* 1979, 2683; (b) Vigneron J.-P.; Jacquet, I. *Tetrahedron* 1976, 32, 939; (c) Jacquet, I.; Vigneron J.-P. *Tetrahedron Lett.* 1974, 2065.

- 263. Yamamoto, K.; Fukushima, H.; Nakazaki, M. J. Chem. Soc. Chem. Commun. 1984, 1490.
- 264. Terashima, S.; Tanno, N.; Koga, K. J. Chem. Soc. Chem. Commun. 1980, 1026.
- 265. Kawasaki, M.; Suzuki, Y.; Terashima, S. Chem. Lett. 1984, 239.
- 266. Kienan, E.; Hafeli, E.K.; Seth, K.K.; Lamed, R. J. Am. Chem. Soc. 1986, 108, 162.
- 267. Brown, H.C.; Cho, B.T.; Park, W.S. J. Org. Chem. 1987, 52, 4020.

^{260.} Asami, M.; Mukaiyama, T. Heterocycles 1979, 12, 499.

 ⁽a) Sato, T.; Gotoh, Y.; Wakabayashi, Y.; Fujisawa, T. *Tetrahedron Lett.* 1983, 24, 4123; (b) Sato, T.; Goto, Y.; Fujisawa, T. *Ibid.* 1982, 23, 4111.

⁽a) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. J. Am. Chem. Soc. 1984, 106, 6709; (b) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. Ibid. 1984, 106, 6717; (c) Noyori, R.; Tomino, I.; Tanimoto, Y. Ibid. 1979, 101, 3129; (d) Nishizawa, M.; Yamada, M.; Noyori, R. Tetrahedron Lett. 1981, 22, 247.



 Table 4.5. Preferred Asymmetric Reducing Agents

Class of Ketones		Proferred Reage	nts (decreasing order of effectiveness)
L Acyclic	a Unhindered	727	2 5-dimethylborolane
1. 11090110	u. Ommuereu	212	B-Inc-9-BBN 6 Khar
		237	T brockij
	b. Hindered	227	2.5-dimethylborolane
		225	IPc ₂ B-Cl
		226	$BH_3 \bullet AMDPB (2:1)$
II. Cyclic		225	IPc ₂ B–Cl
		226	$BH_3 \bullet AMDPB$ (2:1)
		231	K-Glucoride
III. Aralkyl	a. Unhindered	212	B-Ipc-9-BBN, 6 Kbar
-		225	IPc ₂ B–Cl
		233	LiAlH ₄ •DBP•EtOH
		234	Binal-H
		236	LiAlH ₄ •diamine
	b. Hindered	231	K-Glucoride
		236	LiAlH ₄ •diamine
		225	IPc ₂ B–Cl
IV. Heterocyclic		212	B-Ipc-9-BBN, 6 Kbar
		212	B-Ipc-9-BBN, neat
		225	IPc ₂ B–Cl
V. α-Halo		212	B-Ipc-9-BBN, neat
		226	BH ₃ •AMDPB (2:1)
		225	IPc ₂ B–Cl
		234	Binal-H
VI. α-Keto esters		212	B-Ipc-9-BBN, neat
VII. β-Keto esters		229	LiBH ₄ •DBC•t-BuOH
		225	IPc ₂ B–Cl
VIII. Acyclic conjugated	enones	234	Binal-H
		Α	LiAlH ₄ •MEP•NEA ^a
		236	LiAlH ₄ •aminobutanol
IX. Cyclic conjugated en	ones	236	LiAlH ₄ •aminobutanol
		В	LiAlH ₄ •MEP•EAP ^b
X. Conjugated ynones		234	Binal-H
		224	NB•Enantrane
		232	LiAlH ₄ •MEP•ArOH
		212	B-Ipc-9-BBN, 6 Kbar
^a A. 232 + LiAlH ₄ + 2-ethylaminopyridine ²⁶⁴ ^b B. 232 + LiAlH ₄ + 2-ethylaminopyridine ²⁶⁵ (R)- for			
2,2-dimethylcyclopentanone to	16% ee (S) for 2-chloroad	cetophenone to 71% ee	(S) for 2-cyclohexen-1-one. ²⁶⁷
[Reprinted with permission fro Copyright © 1987 American C	m Brown, H.C.; Park, W.S hemical Society.]	S.; Cho, B.T.; Ramacha	ndran, P.V. J. Org. Chem., 1987, 52, 5406.

Development of chiral additives for asymmetric reduction is on-going. The, reduction of acetophenone with a **238**-borane complex gave **239** in 88% yield and 92% ee (R).²⁶⁸ Reduction of acetophenone with borane, catalyzed by 0.1 equivalents of oxazaborolidine **240**, gave a >95% yield of the (–)-enantiomer [**241**; 84% ee, (S)].²⁶⁹ When oxazaborolidine-nickel boride complex (**242**) was mixed with borane, acetophenone was reduced to **241** with 94% ee.²⁷⁰ Note that the use of oxazaborolidine reagents for the enantioselective reduction of ketones was previously described.²⁷¹ Oxaborolidines derived from amino alcohols of (1R)-camphor have also been used as catalysts.²⁷² Bolm et al. showed that hyperbranched dendritic amino acids such as **243** (much more highly branched dendrimers were also used) gave reduction when mixed with a borane-dimethyl sulfide complex. In this example, dendritic amino acid **243** reduced acetophenone under these conditions to **239** in 78% yield and 89% ee (R).²⁷³



4.7.B. Selectivity in the Reduction of Carbonyl Derivatives Containing a Stereogenic Carbon

As seen in Section 4.7.A, chiral reagents prepared from hydrides gave reasonable diastereoselectivity and the % ee ranged from poor to excellent. When the prochiral center is in a molecule that already contains a stereogenic center, reduction generates diastereomers, as mentioned above with the formation of 200 and 201 from 199. Two general cases are illustrated by the reduction of 244 or 247. In the former case, 244 contains a stereogenic

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- 270. Molvinger, K.; Lopez, M.; Court, J. Tetrahedron Lett. 1999, 40, 8375.

^{268.} Sato, S.; Watanabe, H.; Asami, M. Tetrahedron: Asymmetry 2000, 11, 4329.

^{271. (}a) King, A.O.; Mathre, D.J.; Tschaen, D.M.; Shinkai, I. in *Reductions in Organic Synthesis. Recent Advances and Practical Applications*, Abdel-Magid, A.F (Ed.), ACS Symposium Series 641, American Chemical Society, Washington, DC, *1996*. pp 98-111; (b) Quallich, G.J.; Blake, J.F.; Woodall, T.M. *Ibid.* pp 112-126.

^{272.} Santhi, V.; Rao, J.M. Tetrahedron: Asymmetry 2000, 11, 3553.

^{273.} Bolm, C.; Derrien, N.; Seger, A. Chem. Commun. 1999, 2087.

center, but it is too far removed from the prochiral center to exert much influence. Note that the absolute configuration of the stereogenic center at C7, in 244, is unchanged in both 244 and 246, and C7 does not influence reduction of the carbonyl moiety. Reduction of this compound will be, more or less, the same as reduction of a ketone with no stereogenic center and the resulting mixture should be close to a 1:1 mixture of syn and anti diastereomers (245 and 246). Ketone 247, however, has a stereogenic center adjacent to the carbonyl and its chirality will exert an influence on the approach of the incoming reagent. Reagents will approach from the face presenting the least amount of steric hindrance. In 247A, approach over the hydrogen atom (the *si* face) will give **249**, but approach over the more hindered methyl group (the *re* face) will give 248 (alcohols 248 and 249 are diastereomers). This analysis assumes that **247A** is frozen into the rotamer shown, which is incorrect of course. This ketone and similar acyclic systems are not locked into a single conformation, and for 247 we can consider two major rotamers with the carbonyl either down (247A in the first analysis) or up (247B) relative to the methyl group on the stereogenic carbon. In both cases, we have also assumed that the carbonyl bisects the H and Me, although many other rotamers are possible. Reduction from the si face in conformation 247B leads to 248, and reduction from the re face gives 249. In both rotamers of 247, the major product of reduction is the one that occurs from the si face, over the less sterically demanding hydrogen atom. However, reduction of rotamer 247A leads to 249 as the major product, whereas reduction of 247B from the *si* face gives 248 as the major product. If there is no control of the rotamer population at the time of reduction, there is little or no stereoselectivity. Good stereoselectivity in a reaction demands that one face (re vs. si) is preferred and also that one rotamer is preferred. Prediction of stereochemistry therefore demands a model that makes assumptions about both.



Models for predicting asymmetric induction in systems containing an adjacent stereogenic center have been discussed by Morrison and Mosher.²⁷⁴ Cram suggested a model for

^{274.} Reference 231, pp 84-132.

asymmetric induction in ketones such as 247, known as Cram's open chain model (Cram's model), or simply Cram's rule.^{275,276} This model *assumes a kinetically controlled reaction* (nonequilibrating and noncatalytic) for asymmetric 1,2-addition to aldehydes and ketones. The three groups attached to the stereogenic center are R_s (small substituent), R_M (middle-sized substituent), and R_L (large substituent). Determining the relative size of the substituents is not always straightforward, since the *largest* group is defined as the most sterically demanding group relative to the other substituents and the incoming reagent. *Ab initio* calculations by Bienz and co-workers showed that anti-Cram selectivity was favored for compounds that possess very large groups, and that silicon-containing compounds showed the same type of selectivity as the carbon analog.²⁷⁷ A typical Cram model is shown as its Newman projection (**250**),



and assumes that the predominant rotamer that mimics the transition state for reduction has the large substituent (R_L) syn- to the R^1 group attached to the carbonyl. The hydride is delivered from the less sterically hindered face (over the smallest substituent R_s) to give 251 as the major diastereomer. Stereoselectivity is determined by the extent of the $O \leftrightarrow R_s$ or $O \leftrightarrow R_M$ interaction with the metal hydride. As the steric bulk between R_S and R_M increases, selectivity improves. If R_s and R_M are close in size, this model predicts little or no selectivity. This model also assumes the $R_L \leftrightarrow R^1$ interaction is minimal, which is not entirely correct.²⁷⁸ As the steric bulk of R^1 increases, the proportion of the anti- product (253) produced by LiAlH₄ reduction of chiral ketone 252 increases (48% when $R^1 = Me$; 52% for $R^1 = Et$; 70% for $R^1 = i$ -Pr; 96% for $R^1 = t$ -Bu). This observation suggests that the $R_s - R_M \leftrightarrow R^1$ rather than the $R_s - R_M \leftrightarrow O$ interaction is important in this model. In a synthesis of the C1-C12 fragment of the tedanolides by Jung and Yoo, L-Selectride reduction of 254 gave a 75% yield of a single diastereomer (255).²⁷⁹ The Cram model (see 254a) has the large group (alkyl chain) syn- to the dioxolane moiety, and delivery of hydride over the small group (H) predicts incorrect product. The anti-Cram model must be used since there are oxygen atoms on the α -carbon in the dioxolane ring, and the anti-Cram model predicts 255.

 ^{275. (}a) Cram, D.J.; AbdElhafez, F.A. J. Am. Chem. Soc. 1952, 74, 5828; (b) Cram, D.J.; Kopecky, K.R. Ibid. 1959, 81, 2748; (c) See also Mengel, A. Reiser, O. Chem. Rev. 1999, 99, 1191.

^{276.} Eliel, E.L.; Wilen, S.H.; Mander, L.N. Stereochemistry of Organic Compounds, Wiley, New York, 1994, p879.

^{277.} Smith, R.J.; Trzoss, M.; Bühl, M.; Bienz, S. Eur. J. Org. Chem. 2002, 2770.

^{278.} Reference 231, p 91.

^{279.} Jung, M. E.; Yoo, D. Org. Lett. 2007 9, 3543.



When the relative difference in size of the groups is negligible, little or no diastereoselectivity is observed. Reduction of **256**, for example, gave a 1:1 mixture of syn- and anti-diastereomers **257** and **258**.²⁸⁰ The R_M/R_L groups are phenyl and 4-methylphenyl and at the reactive center (the carbonyl), the methyl group of the *p*-tolyl moiety is rather far away. To the approaching hydride reagent phenyl and tolyl are virtually identical in size when analyzed by the Cram model.



MOLECULAR MODELING: Stereoselectivity of Reductions of Flexible Molecules

Anticipating product distributions in the reduction of flexible (acyclic) ketones is complicated by the need to assign a preferred conformation. A good example is provided by the LAH reduction shown below, which gives a 1:2.5 mixture of the RSR:RSS diastereomers.



The rigid three-member ring attached by a stereogenic center to the carbonyl group may assume one of three possible conformers. In addition, the CC bond connecting the carbonyl to the cyclohexyl ring may be either *equatorial* or *axial* (on the cyclohexyl ring). That is, there are six different (3 x 2) conformers in total. However, quantum chemical calculations suggest that of these six, two nearly-equally-populated conformers account for >90% of the overall distribution. Both of these key conformers must be examined to establish the stereochemical preference for the reduction.

Identifying the lowest-energy conformer(s) of a flexible molecule with more than one degrees of (conformational) freedom is beyond the scope of this problem. This topic is considered in a collection of "mirror problems" included with this text and intended for use with *Spartan Student* or *Spartan*.

^{280.} Stocker, J.H.; Sidisunthorn, P.; Benjamin, B.M.; Collins, C.J. J. Am. Chem. Soc. 1960, 82, 3913.

MOLECULAR MODELING: Stereoselectivity of Reductions of Flexible Molecules, con't.

The LUMO maps for the two important conformers noted above are shown. These are depicted as transparent models, allowing the underlying structures (conformers) to be seen. It is not surprising that both conformers are *equatorially* substituted. Once you are oriented with regard to the structure, you can switch to solid models, allowing the maps to be seen more easily. *Click* on one of the maps and then select *Solid* for the **Style** menu at the bottom of the screen. For each conformer, identify the face of the double bond that is more susceptible to hydride attack by examining the intensity of the blue area on each face, and assign the stereochemistry of the product. By convention, regions on the accessible surface where the LUMO is most concentrated, and most susceptible to attack by an electron donating species such as LAH, are colored "blue", and regions where it is least concentrated and more likely to be electron donating are colored "red". Therefore, the face with the more blue should be the preferred face for delivery of hydride, and lead to the major diastereomeric product. Is the favored product according to the LUMO map the same for both conformers? If it is, is it the product formed in greater amount?

MOLECULAR MODELING: Stereochemistry of Nucleophilic Additions to Flexible Molecules

Assignment of stereochemistry in nucleophilic additions involving rigid molecules (bicyclic, polycyclic, and highly substituted monocyclic molecules) is a straightforward application for a molecular model such as the LUMO map. However, very few molecules are rigid, but instead exist as an equilibrium mixture of two or more different conformers. For reduction of an acyclic ketone, for example, *the appropriate conformer must be identified prior to use of a LUMO map*. It is also known, however, that the presence of a stereogenic center proximal to the reactive center often leads to highly diastereoselective reactions. Consider the LAH reduction of 4-isopropyl-3-heptanone, which gives one diastereomeric alcohol as a major product.



To find the appropriate conformer, it must be recognized that 4-isopropyl-3-heptanone has five rotatable carbon-carbon bonds, which means that there may be as many as 243 (3^5) different conformers. Calculations show that a dozen conformers are required to account for 90% of the room-temperature equilibrium distribution, and three conformers are found to account for 50%. (Identifying the lowest-energy conformer of a flexible molecule with multiple degrees of conformational freedom is beyond the scope of this problem. This topic is considered in a collection of "mirror problems" included with this text, and intended for use with *Spartan Student* or *Spartan*.)

LUMO maps for the three "most important" conformers are provided on screen. Examine each map in turn and identify the face of the double bond that is more susceptible to nucleophilic attack (more blue). Does the preference change with conformer? Can you make a clear "prediction" of the stereochemistry of the product? Is this consistent with the experimental result (see above)?
MOLECULAR MODELING: Stereochemistry of Reduction of Diketones

Sodium borohydride reduction of **95** gives **96**, the product which results from selective reaction at the non-conjugated carbonyl group (see section 4.4.A).



The observed preference for **96** would not have been anticipated by examination of a LUMO map, simply because the LUMO in **95** is primarily concentrated on the conjugated carbonyl group. This brings up an important point. The LUMO map is only applicable as an indicator of nucleophilic reactivity where the LUMO corresponds to the "reactive site". Other unoccupied molecular orbitals (LUMO+1, LUMO+2, etc.) may instead be appropriate. The only way to be certain is to examine the first few unoccupied orbitals until the relevant orbital is uncovered. In this particular case, it is the next higher-energy unoccupied orbital (LUMO+1), and the "LUMO+1" map is the appropriate indicator.

First examine the LUMO map for **95** (left). On which carbonyl group is the LUMO primarily localized? Next, examine the LUMO+1 map (right). On which carbonyl group is it primarily localized? Which face of the carbonyl group is should be more susceptible to attack by the nucleophilic hydride, that is, which face is more blue? Is the face that leads to the observed product?

When an oxygen, sulfur, or nitrogen is attached to the carbon α to the carbonyl, the metal of the hydride can coordinate (chelate) to both the heteroatom and the carbonyl oxygen, which effectively locks the molecule into a single rotamer. The Cram designations of large, medium and small no longer have the same meaning. When such a cyclic chelated structure can be formed, the model is changed to the **Cram cyclic model** (more commonly called the **Cram chelation model**).^{280,281,275c} When a hydroxyl group, an ether, amino, amide, thiol or thioether group is in the α -position, chelation to that group makes it eclipse the carbonyl, as shown in complex **259**. Delivery of hydride from the less hindered face (over R_s) predicts the major diastereomer, **260**. In one example, the ether-oxygen in the eight-membered ring in **261** along with the carbonyl-oxygen formed the chelated complex **262**, and subsequent quenching with water led to **263** in 48% yield as the single diastereomer shown in Holmes and co-worker's synthesis of (+)-laurencin.²⁸²

^{281.} Cram, D.J.; Wilson, D.R. J. Am. Chem. Soc. 1963, 85, 1245.

^{282.} Burton, J.W.; Clark, J.S.; Derrer, S.; Stork, T.C.; Bendall, J.G.; Holmes, A.B.J. Am. Chem. Soc. 1997, 119, 7483.



The selectivity in this model, sometimes called **anti-Cram** selectivity, will depend on the reagent, the chelating ability of the substituent, the coordinating ability of the solvent as well as the relative size of the substituents (R_s and R_L). Morrison and Mosher presented data for these systems that included reduction of **263** to an 88:16 mixture of **264** and **265**.^{283,280} The presence of the methoxy group in **263** led to a chelated intermediate, and the Cram cyclic model predicts the correct diastereoselectivity. In derivatives where the hydroxyl is blocked (protected, see chap. 7), the reduction proceeds with normal Cram selectivity.²⁸⁴ In general, a

hydroxyl substituent is capable of coordinating via a hydrogen bond and should be more tightly bound than when the hydroxyl is blocked (as in an OMe group). The distance between the chelating group and the carbonyl is an important consideration.

Oishi²⁸⁵ and co-workers studied the diastereoselectivity of α -alkoxy and α -hydroxy ketones as they reacted with several reducing agents.²⁸⁵ When R¹ = H, there was a distinct preference for the anti (erythro) diastereomer **265** when Zn(BH₄)₂ was used for reduction. The anti product was the major one with LiAlH₄, but the reaction was less selective. The Cram chelation model

for the anti transition state (266) to give 265 was favored over the model for syn selectivity (where delivery over the methyl group would give 264). When hydroxyl was replaced with a bulky silyl ether ($R^1 = \text{SiPh}_2t$ -Bu), the selectivity changed from anti to syn. Chelation was diminished and Cram's rule (267) must be used to predict the correct syn-selectivity. In





^{283.} Reference 231, pp 100-108.

^{284.} Yamada, S.; Koga, K. Tetrahedron Lett. 1967, 1711.

^{285.} Nakata, T.; Tanaka, T.; Oishi, T. Tetrahedron Lett. 1983, 26, 2653.

section 4.4.B, excellent diastereoselectivity was obtained in the zinc borohydride reduction of **121**, giving **122** as the major product. Oishi examined the reduction of β -keto esters such as **268** (R¹ = Ph, R² = Me) with zinc borohydride and found a preference for the syn-product (**269**, R¹ = Ph, R² = Me) over the anti-product (**270**), of more than 99:1 (98% yield).¹⁵⁶ The analogous methyl ketone (**268**, R¹ = Me, R² = Bn) gave only a 2:1 mixture of **269/270** under identical reaction conditions.¹⁵⁶ Zinc coordinated both the carbonyl of the ester moiety and the oxygen of the prochiral carbonyl group. Hydride was delivered from the less hindered face (over hydrogen), which is the *si* face when R¹ is phenyl and the *re* face when R¹ is methyl (referring to **268**).

$$R^{1} \underbrace{\bigvee_{O}}_{CO_{2}R^{2}} CO_{2}R^{2} \xrightarrow{1. Zn(BH_{4})_{2}, \text{ ether}}_{2. H_{3}O^{+}} R^{1} \underbrace{\bigvee_{OH}}_{OH} CO_{2}R^{2} + R^{1} \underbrace{\bigvee_{i=0}}_{OH} CO_{2}R^{2}$$

The presence of an α -alkoxy substituent does not always lead to anti-Cram selectivity. Reduction of **271a** gave 82% of the syn diastereomer, **272**.²⁸⁶ Analysis of the Cram cyclic model for **271** (see **273**) gives an incorrect prediction of the anti-diastereomer (**274**) as the major product. The normal Cram model (see **271b**) predicts the correct syn-diastereomer (**272**) but, in reality, reduction requires that the alkoxy substituent at the C3 position be coordinated with the metal of the reducing agent. In **273**, a five-membered cyclic transition state is possible via coordination with the benzyloxy group. In **275**, coordination of the reagent to the 3-alkoxy substituent leads to a six-centered cyclic transition state, with delivery of hydride from the less hindered methyl face leading to **272**. With hindered reducing agents such as tri-*tert*-butoxyaluminum hydride, **275** is preferred to **273**. As the nature of the alkoxy substituent changes, it is clear that the model used to predict the major diastereomer may change.



 Hoagland, D.; Morita, Y.; Bai, D.L.; Märki, H.-P.; Kees, K.; Brown, L.; Heathcock, C.H. J. Org. Chem. 1988, 53, 4730.

The reduction of **271a** illustrated that chelating substituents at the carbon β to a carbonyl can influence the diastereoselectivity of hydride reductions, which is particularly important for the reduction of 1,3-diketones and β -ketoesters. When the α -substituent is a halogen, however, the open-chain model does not predict the correct results nor does the chelation model. Cornforth et al.²⁸⁷ suggested that the electron pairs on the carbonyl oxygen and on the halogen repel and assume an anti-conformation, as in **276**. In effect, the halogen becomes R_L with delivery of hydride over the smallest group, which has come to be called the **Cornforth model**. Reduction of **276** gave a 75:25 mixture of **277** and **278**, and the Cornforth model predicted **277** as the major product.²⁸⁸ Note that Evans and co-workers²⁸⁹ studied the aldol reaction (sec. 9.4.A) between methyl-substituted *Z*- and *E*-enolate anions (sec. 9.2.C) and α -oxygen-substituted aldehydes, and concluded that the diastereoface selectivity (sec 9.5.A) was more consistent with the Cornforth model.



The Cram open-chain model assumed the presence of a reactive species that led to a higher energy eclipsed conformation in the final product. The Cram open-chain model fails to predict the correct diastereoselectivity for many acyclic molecules that contain heteroatom substituents.²⁹⁰ The Cram model also fails to predict the correct diastereomer when the relative size of R_s and R_M is close. Karabatsos introduced a new model, in an attempt to correct the deficiencies of the Cram model.²⁹¹ He assumed a *reactant-like transition state* that showed little bond breaking or bond making. The rotamer chosen for the model showed the groups on

the stereogenic carbon to be aligned as in a normal sp^3-sp^2 bond, which led to three rotamers that were considered by the **Karabatsos model** (**279-281**). The incoming reagent was assumed to approach over the R_s group.²⁹² Note that reaction over R_s in all three rotamers gives a product with an anticonformation. Karabatsos showed that **281** was



^{287.} Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. J. Chem. Soc. 1959, 112.

- 288. Bodot, H.; Dieuzeide, E.; Jullien, J. Bull. Soc. Chim. Fr. 1960, 27, 1086.
- 289. Evans, D.A.; Siska, S.J.; Cee, V.J. Angew. Chem. Int. Ed. 2003, 42, 1761.

^{290.} Reference 231, p 118.

^{291.} Karabatsos, G.J. J. Am. Chem. Soc. 1967, 89, 1367.

 ⁽a) Karabatsos, G.J.; Hsi, N. J. Am. Chem. Soc. 1965, 87, 2864; (b) Karabatsos, G.J.; Hsi, N. Tetrahedron 1967, 23, 1079; (c) Karabatsos, G.J.; Krumel, K.L. Ibid. 1967, 23, 1097; (d) Karabatsos, G.J.; Fenoglio, D.J.; Lande, S.S. J. Am. Chem. Soc. 1969, 91, 3572. (e) Karabatsos, G.J.; Fenoglio, D.J. Ibid. 1969, 91, 1124, 3577.

favored over **279** by 0.8 kcal mol⁻¹ (3.35 kJ mol⁻¹) when $R_s = H$ and $R_M = Me$. The selectivity of a reduction was assumed not to be dependent on the higher energy **279**, but rather on rotamers **280** and **281**. It was then assumed that the destabilizing $O \leftrightarrow R_L$ and $O \leftrightarrow R_M$ energy interactions in these two rotamers would determine the diastereoselection for the reaction. Although this model is inadequate when R_s is large, or when applied to cyclic molecules, it offers advantages over the Cram model in some applications.

Felkin and Anh proposed an alternative model that gave somewhat better results in these systems.^{293,294} The model was based on several assumptions. (1) the transition states are reactantlike (2) the previous eclipsed models introduce significant torsion strain in the partial bonds of these transition states (3) the important steric interaction in these transition states involves the group attached to the prochiral center and the incoming group (4) polar effects stabilize the transition states in which the separation of the incoming group and any electronegative substituent at the α -carbon is greatest and destabilize the others. Felkin concluded that models 282 and 283 were the most important. The use of these structures to predict diastereoselectivity is called the Felkin-Anh model.²⁹³ The correctness of this model has been called into question, based on calculations done by Bientz and co-workers.²⁹⁵ "According to our calculations, the Felkin-Anh model does not correctly represent the modes of reaction on the course of nucleophilic attack to α -chiral carbonyl compounds. For typical reactions, the two transition states with the M and L groups arranged 'inside' and 'anti' are the key structures, and discrimination is due to the repulsive interactions of the incoming nucleophiles with the 'inside' groups. For compounds with very large groups L, the relevant transition structures are those with this L group placed 'anti' (Felkin-Anh conformations). For the discrimination, the interaction of the incoming nucleophile with the 'inside' rather than the 'outside' group is relevant. This leads to anti-Cram selectivity for such compounds. Acylsilanes should show the same selectivities as the related ketones. The selectivities, however, are expected to be lower and the relevant transition structures might differ from those of the carba analogs."295

When R_M and R_S are relatively close in size, the Felkin-Anh model predicts modest to poor selectivity because there is little difference in the destabilizing $R_M \leftrightarrow O, R_S \leftrightarrow O$ or $R_S \leftrightarrow R^1$, $R_M \leftrightarrow R^1$ interactions. As R_M or



 R^1 increases in steric bulk, the increased $R_M \leftrightarrow R^1$ destabilizing interaction in **283** will favor **282**.²⁹⁶ Reduction of **284** with LiAlH₄ was shown to give a 2:1 mixture of **285** and **286**.²⁹⁷ For

^{293. (}a) Chérest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* 1968, 2199; (b) Chérest, M.; Felkin, H. *Tetrahedron Lett.* 1968, 2205; (c) Anh, N.T.; Eisenstein, O. *Nov. J. Chem.* 1977, 1, 61.

^{294.} Reference 276, p 881.

^{295.} Smith, R.J.; Trzoss, M.; Bühl, M.; Bienz, S. Eur. J. Org. Chem. 2002, 2770.

^{296.} Reference 231, p 116.

^{297.} Cram, D.J.; McCarty, J.E. J. Am. Chem. Soc. 1954, 76, 5740.

an analysis of this reduction, the two models of interest are **287** (which predicts **285**) and **288** (which predicts **286**). Note that the analogous 3D model shown above each 2D model). The Me \leftrightarrow Me interaction in **288** is greater than the analogous H \leftrightarrow Me interaction in **287**, making **287** more favorable, and delivery of hydride via **287** predicts **285** as the major product.



The Felkin-Anh and Cram models are best applied to acyclic systems. Problems arise when any of these models are used to predict the products generated by the reduction of cyclic ketones. These problems will be analyzed and new models for predicting diastereoselectivity in the reduction of cyclic molecules will be discussed in Section 4.7.C. Table 4.6 attempts to compare the two most-used models, the Cram and Felkin-Anh, with the LUMO map approach using calculations. All experimental data are taken from the literature,^{275c} and the major diastereomer expected from each substrate (A or B) is predicted using each model. It is clear that the Cram and Felkin-Anh models give similar predictions and are generally correct, but both fail when there are oxygen substituents at the α -position. In such cases, the anti-Cram or anti-Felkin-Anh model are used to make predictions. Note that when the -NBn₂ group is at the α -position, the anti-models lead to incorrect predictions. The LUMO maps generally give good predictions when compared to the experimental results, with the exception of the α -chloro substituent. For the α -methoxy derivative, the LUMO map predicts the correct diastereomer, but does not predict the outstanding selectivity that was observed in this reaction. LUMO maps are easily obtained, and offer a good model for predicting diastereoselectivity, and can be used in addition to the Cram, anti-Cram or Felkin-Anh models.

Solvent can play a significant role in the selectivity. The reaction of phenylmagnesium bromide with **284**²⁹⁸ (a Grignard reaction, sec 8.4) led to alcohol products **285** and **286**, and the ratio of *S:R* to *S:S* product was 73:27 in DME, 61:39 in THF, 51:49 in dioxane, and 36:64 in ether. Solvation of the metal in this case is undoubtedly responsible to changes in selectivity, but the result calls into question the efficacy of predictive models. This particular result suggests that model **287** predicts the correct major product in DME and THF, but the anti-Felkin-Anh model predicts the result in ether.²⁹⁸ Therefore, these models must be used with care, and solvent effects for a given system should be examined by searching the literature making predictions prior to running the experiment.

^{298.} Perez-Ossorio, R.; Perez-Rubalca, A.; Quiroga, M.L. Tetrahedron Lett. 1980, 21, 1565.

 Table 4.6. A Comparison of the Cram and Felkin-Anh Models with LUMO Maps, Against

 Experimentally Determined Ratios^{275c} of Diastereomers Using Various Nucleophiles.



4.7.C. Selectivity in Reduction of Monocyclic Molecules

Predictions of stereochemistry for *cyclic* ketones using the Cram or Felkin-Anh models are generally unreliable. Reduction of 2-methylcyclopentanone (see Table 4.7)²⁹⁹ can be used to illustrate the difficulty. Model **289** is an approximation of the Cram model for 2-methylcyclopentanone, and it predicts the cis isomer to be the major product of hydride reduction. Analysis of cyclic ketones shows that fitting them to the Cram model requires distortion of the ring away from the low energy conformations (chair or envelope for six- and five-membered rings, respectively). The Felkin-Anh model for 2-methylcyclopentanone (**290**) has similar problems but less distortion of the ring is required, although it also predicts the cis product. Reductions of actual molecules (see Table 4.7) show that the trans isomer (**292**) is

^{299.} Reference 231, p 119.

favored except when very bulky reducing reagents are used. Both the Cram and Felkin-Anh models gave incorrect predictions.



 Table 4.7. Hydride Reduction of 2-Methylcyclopentanone

$\bigwedge^{O}_{Me} \xrightarrow{\text{reduction}}$	OH + trans	OH Whe cis
<u>Reagent</u>	% <u>trans</u>	<u>% cis</u>
$NaBH_4{}^a$	74	26
LiAlH ₄ ^{b,c}	76	24
$B_2H_6^e$	69	31
LiAlH(OMe) ₃ ^{a,b}	56	44
LialH(OEt)3 ^b	77	23
LiAlH(Ot-Bu) ₃ ^{a,b}	72	28
$L_1(mesityl)_2BH_2^{e}$	$\frac{2}{1}$	98 -
L-Selectride ^d Li(siamyl) ₃ BH ^d	1.5 0.5	98.5 99.5
Reprinted by courtesy of Professor H.S. Asymmetric Organic Reaction. 1976, p. 119.]	James D. Morrison from s, American Chemical So	Morrison, J.D.; Mosher, ociety, Washington, DC

a Ref. 300 b Ref. 301 c Ref. 302 d Ref. 303 e Ref. 304

The actual experimental results can be explained by using two envelope conformations available to 2-substituted cyclopentanones, **291** and **292** (sec. 1.5.B). In **291**, approach of a reagent to the carbonyl at an angle of ~ 110° (the **Bürgi-Dunitz trajectory**, sec. 6.6.A)³⁰⁵ leads to an interaction with H_a (path *b*), making path *a* preferred and this leads to the trans product. Remember that this angle assumes a late transition state in which the approach angle approximately mimics the tetrahedral angles of the sp³-hybridized carbon found in the alcohol products. This result is apparently contradicted by **292**, where approach via path *a* is inhibited by the R group. Since the R group will be pseudo-equatorial in the lowest energy conformation (as in **291**), this model is used to predict the major diastereomer in reactions of cyclopentanone derivatives. Indeed, reduction via path *a* in **291** leads to the correct stereochemical predictions in Table 4.7, except when bulky reducing agents are employed. Structure **293** is a 3D model of **292** (R = Me), showing the steric influence of the group on approach to the acyl carbon.

^{300.} Umland, J.B.; Jefraim, M.I. J. Am. Chem. Soc. 1956, 78. 2788.

^{301.} Brown, H.C.; Deck, H.R. J. Am. Chem. Soc. 1965, 87, 5620.

^{302.} Ashby, E.C.; Sevenair, J.P.; Dobbs, F.R. J. Org. Chem. 1971, 36, 197.

^{303.} Brown, H.C.; Bigley, D.B. J. Am. Chem. Soc. 1961, 83, 3166.

^{304.} Caro, B.; Boyer, B.; Lamaty, G.; Jaouen, G. Bull. Soc. Chim. Fr. 1983, Pt. 2, 281.

^{305.} Bürgi, H.B.; Dunitz, J.D.; Lehn, J.M.; Wipff, G. Tetrahedron 1974, 30, 1563.

Inspection of a LUMO map for 2-methylcyclopentanone shows a more intense color for the carbonyl carbon on the same face as the methyl group, suggesting a preference for the *trans*-alcohol, consistent with Table 4.7, although **291** gives an incorrect prediction when bulky reagents such as Selectride are used.



As the α -substituent in 2-substituted cyclopentanones increases in size from methyl to *tert*butyl (see **295**), path *a* becomes less favored and lower selectivity is observed as seen in Table 4.8.³⁰⁴ The reason for this is shown for the *tert*-butyl derivative (see **294**), where the methyl groups impose greater hindrance to approach via path *a*. The LUMO map of **294** also indicates less selectivity. Even with this very bulky *tert*-butyl group, essentially a 1:1 mixture of stereoisomers is obtained upon reduction. For clarity, it must be emphasized that **291**, **292**, and **294** are distorted as drawn in a stylized envelope conformation (compare with **293**).

Table 4.8. Lithium Aluminum Hydride Reduction of 2-Substituted Cyclopentanones



MOLECULAR MODELING: Nucleophilic Attack on Substituted Cyclopentanones

A LUMO map colors a surface of electron density (indicating overall molecular size and shape) with the (absolute) value of the lowest-unoccupied molecular orbital (the LUMO). By convention, blue regions on the surface indicate where the LUMO is most concentrated. Examine maps for 2-methylcyclopentanone (left) and 2-*tert*-butylcyclopentanone (right), and for each assign the favored direction of attack by a nucleophile, that is, the side on which the LUMO is more concentrated. Which compound would be expected to show greater selectivity? Are your results in line with the experimental data shown above?

The Cram model is a poor model for reduction of cyclohexanone derivatives. Antiperiplanar hyperconjugative effects have been invoked to explain the observed results. The Felkin-Anh

H 299 Η

OH

model suggests an interaction such as that shown in **296**.³⁰⁶ Cieplak put forth an alternative proposal (see **297**, the **Cieplak model**).³⁰⁷ The incipient bond (the one being formed) was found to be electron deficient. This model has led to some controversy, and a so-called exterior frontier orbital extension model has been proposed to explain the selectivity.³⁰⁸

298

1. LiAlH₄

2. H₃O



300

The stereoselectivity associated with substituted cyclohexanones can be shown using the reaction of 4-tert-butylcyclohexanone (298) with lithium aluminum hydride or sodium borohydride, which gave the trans-alcohol (299) as the major product (92% and 80%, respectively) via axial attack (path a).³⁰⁹ The bulky *tert*-butyl group at C4 in **298** effectively locks the molecule into that chair conformation (sec. 1.5.D). The Cram model or the Felkin-Anh model predict path b as the major pathway (to give **300**), which is incorrect. A more useful perspective for this analysis is a model represented by 298, which suggests that approach via path b is encumbered by the axial hydrogens on the bottom face of the molecule. An important aspect of these models is the trajectory of approach for the hydride. The angle of approach will be close to 110° (see above)³⁰⁵ and over the π bond of the carbonyl (as seen in **298**). This angle of approach will exacerbate the steric problems posed by the axial hydrogens at C2 and C6 for path b and the axial hydrogens at C3 and C5 for path a. In simple cyclohexanone derivatives, path a is preferred. When the α -carbon is substituted, as in **301**, path *a* (to give **302**) is preferred to path b (which gives 303) unless R is very large, as shown in Table 4.9. 304,302 Analysis of the intensities of the carbonyl carbon in a LUMO map of 2-methylcyclohexanone indicates that there is a preference for path *a* (see 301). Structures 304a and 304b are 3D-models for 2-methylcyclohexanone, showing the steric impedance imposed by both an axial methyl group (304b, blocking path b) and an equatorial methyl group (304a). As the steric bulk at C2 is increased, approach from path a is somewhat inhibited, leading to increasing amounts of the cis-product (via path b). It is interesting to note that $LiAlH(OMe)_3$ gives more cis-product than LiAlH(Ot-Bu)₃. Generally, smaller reagents give more axial attack (path a) and larger reagents give more equatorial attack (path b). In their monograph, Morrison and Mosher arranged the

^{306. (}a) Reference 282; (b) Ahn, N.T.; Eisenstein, O.; Lefour, J.-M.; Traàn Huu Daàu, M.E. J. Am. Chem. Soc. 1976, 95, 6146; (c) Ahn, N.T.; Eisenstein, O. Nouv. J. Chim., 1976, 1, 61.

^{307. (}a) Cieplak, A.S. J. Am. Chem. Soc. 1981, 103, 4540; (b) Reference 276, pp 882-883.

^{308.} Tomoda, S.; Senju, T. Tetrahedron 1999, 55, 3871.

^{309. (}a) Richer, J.-C. J. Org. Chem. 1965, 30, 324; (b) Richer, J.-C.; Perrault, G. Can. J. Chem. 1965, 43, 18.

relative size of hydride reagents as follows.³¹⁰

	301 re	$\xrightarrow{\text{OH}}^{R} + 302$	OH 303
<u>R</u>	Reagent	<u>% 302 (axial attack)</u>	% 303 (equatorial attack)
Me	LiAlH ₄ /THF	76	24
	NaBH ₄ / <i>i</i> -PrOH	70	30
	LiAlH(Ot-Bu)3/THF	70	30
	LiAlH(OEt)3/THF	74	26
	LiAlH(OMe)3/THF	31	69
Et	NaBH ₄ / <i>i</i> -PrOH	65	35
<i>i</i> -Pr	LiAlH ₄ /THF	63	37
	NaBH ₄ / <i>i</i> -PrOH	50	50
t-Bu	LiAlH ₄ /THF	42	58
	NaBH ₄ / <i>i</i> -PrOH	50	50
	LiAlH(OMe) ₃ /THF	36	64
	LiAlH(Ot-Bu) ₃ /THF	46	54
Reprinted Copyright	in part with permission from Ash 1971 American Chemical Societ	nby, E.C.; Sevenair, J.P.; Dobbs, F. y.	R. J. Org. Chem. 1971, 36, 197.

Table 4.9. Hydride Reduction of 2-Substituted Cyclohexanone Derivatives, 301

 $LiAlH_4 < LiAlH(OtBu)_3 < NaBH_4 < KBH_4 < LiAlH(OMe)_3$ (sec. 4.3) $< Ip_2BH$ (sec. 5.4.B)



Substituents at C3 or C5 also have a significant effect on the approach of reagents to the carbonyl of cyclohexanone derivatives. Using a model similar to the 2-substituted cyclohexanones, reduction of 3-methylcyclohexanone can proceed via path *a* or path *b* (see **305a**). Since the axial methyl group imposes steric hindrance to path *a*, there is a preference for path *b*. It is cautioned that the lower energy chair conformation of 3-methylcyclohexanone is probably **305b** rather than **305a**. Attack via path *b* in **305a** will give the cis product, but note that attack along the preferred path *a* in **305b** also gives the cis product. If we use **305a** as the standard model, then path *b* is preferred. As shown in Table 4.10^{302,311} for 3,3,5-trimethylcyclohexanone (**306**), an *axial* methyl group at C3 of a cyclohexanone blocks path *a* (to give **308**) and the major product is via path *b* to give **307**. The preferred mode of attack is path *b* to give the trans

^{310.} Reference 231, pp 123-124 and citations, 38, 55 and 56 therein.

^{311.} Haubenstock, H.; Eliel, E.L. J. Am. Chem. Soc. 1962, 84, 2363, 2368.

alcohol, **308**. As the size of the hydride reagent increases, path b is more highly favored.

$\begin{array}{c} Me \\ Me \\ Me' \\ Me' \\ 306 \end{array}^{a} \xrightarrow{\text{reduction}} M$	1e + H + H + H = 307	+ Me H Me H Me 308
Reagent	<u>% 307</u>	<u>% 308</u>
$LiAlH_4$	52	48
LiAlH(OMe) ₃	75	25
LiAlH(OEt) ₃	83	17
LiAlH(Ot-Bu)3	73	27
NaBH ₄ /EtOH	67	33
NaBH ₄ /aq. MeOH	71	29
KBH ₄ /ag. MeOH	71	29
NaBH(OMe) ₃ /aq/ MeOH	65	35
NaBH(Oi-Pr),/diglyme	77	23

 Table 4.10.
 Selectivity in Hydride Reductions of 3,3,5-Trimethylcyclohexanone (306)

De Maio et al. studied the stereochemistry and relative rates of k_{ax} and k_{eq} for acyl addition reactions of 5-substituted adamantan-2-ones.³¹² This kinetic data did not fit current theories of π face diastereoselection. Their studies suggest that k_{ax}/k_{eq} measurements do not adequately indicate what is happening on the two sides of a stereogenic center. In addition, they found that axial reactivity always increases with increasing electronegativity of the substituted at C5 and that k_{eq} changes depend on the conformation of that group and on reaction conditions. In their words: "Simple theories such as those based on dipole-dipole interactions are unable to explain such as behavior, nor can theories based on ground state MO calculations."³¹²



^{312.} Di Maio, G.; Solito, G.; Varì, M.R.; Vecchi, E. Tetrahedron 2000, 56, 7237.

4.7.D. Stereoselectivity in the 1,2-Reduction of Cyclohexenone Derivatives

The conformational problems of cyclohexene derivatives are somewhat different than those observed with cyclohexanone or cyclohexane derivatives. The presence of the alkene moiety effectively flattens four carbons of the ring, making the steric interactions of substituents with an incoming reagent different, relative to cyclohexanone derivatives. The most abundant conformations of cyclohexenone derivatives are **309** and **310**. The first problem that arises in conjugated derivatives is the competition of 1,2- with 1,4-addition for many reducing agents,

discussed in previous sections. In this section only products arising from 1,2-reduction will be discussed. It appears that the C2 group (R^1) offers little interference to either path *a* or *b* unless it is very large. The R^2 group, however, caninhibit approach by path *a* if sufficiently large and a large R^4 may inhibit approach by path *b*.



The sodium borohydride-cerium chloride reagent (Luche reagent) gave selective 1,2-reduction of conjugated ketones in section 4.4.B. The sensitivity of the cyclohexenyl system to steric blocking when substituents are present at C5 or C6 is shown by reduction of **311**, which showed a preference for **313** over its diastereomer **312**³¹³. Analysis of carbonyl region in a LUMO map of **311** shows a more intense blue color on the face marked path *b*, consistent with that face being more accessible and formation of **313** as the major product. A 3D model of **311** is provided to show the stereochemical relationships.



4.7.E. Selectivity in the Reduction of Bicyclic and Polycyclic Derivatives

As with monocyclic ketones, bicyclic ketones show excellent diastereoselectivity upon reduction with hydride reagents. This selectivity is clearly observed in the reduction of bicyclo[2.2.1] heptan-2-one (**314**, norbornanone) and 7,7-dimethylbicyclo[2.2.1]heptan-2-one (**316**). The exo face (path *a* in **314A**) is usually preferred, leading to the endo alcohol **315**. The endo

^{313.} Crimmins, M.T.; O'Mahoney, R. J. Org. Chem. 1989, 54, 1157.

hydrogens (H_a in **314A**) provide steric encumbrance and analysis of a LUMO map of **314B** indicates that path *a* is more accessible, consistent with the observed exo-attack. Approach of a reagent to the carbonyl at an angle of 110° brings the reagent into close proximity to this hydrogen. The exo face appears somewhat hindered but is actually less hindered than the endo face. When a methyl group blocks the exo face (path *a*) (see model **316B**), attack by path *b* is preferred and the exo alcohol (**317**) is the major product. Analysis of a LUMO map of **316B** reveals that path *b* is preferred. In all [2.2.1]-, [2.1.1]-, and [2.2.2]-bicyclic ketones of this type, the major product is predicted by the extent of steric hindrance at the exo face (exo attack with no substituents on the bridge, as in **314**).^{314,302,303} When the bridge has substituents (see **316**), endo attack is generally preferred.



MOLECULAR MODELING: Nucleophilic Attack on Norbornanone

It is known that nucleophilic addition to a carbonyl requires that the nucleophile approach the carbonyl carbon from an angle of $\sim 110^{\circ}$ (the "*Bürgi-Dunitz trajectory*"). Where the two faces of the carbonyl group are different, the angle of approach must be considered to determine which is more sterically hindered. Examine a space-filling model for norbornanone (left). Considering the approach angles (*a*) and (*b*), which face of the carbonyl carbon appears to be more encumbered? If steric factors dominate the reaction, what alcohol should result from addition of hydride to norbornanone?

Next, examine the LUMO map for norbornanone (right). This has been displayed in "transparent" mode, allowing you to see the underlying structure. It can be displayed as a solid by *clicking* on the map and selecting *Solid* from the **Style** menu at the bottom of the screen. The "blue regions" of the map indicate maximum concentration of the LUMO on the accessible surface of the molecule, and the "red regions" minimum concentration. The bluest region is most susceptible to attack by the nucleophilic hydride. According to the LUMO map, which face is more likely to be attacked by a nucleophile? Is this the same face as suggested by steric preferences?

When edge-fused bicyclic systems (bicyclo[m.n.0]) are examined, as in Table 4.11,³⁰⁴ they

^{314.} Wheeler, O.H.; Mateos, J.L. Can. J. Chem. 1958, 36, 1431.

behave very similarly to monocyclic ketones. Reduction of decalone (**318**) and indanone (**319**), for example, occurred primarily from path a as shown. In this table, the axial alcohol results from equatorial attack by the hydride and the equatorial alcohol results from axial attack by the hydride. These results show that axial attack (path *a*) is preferred in [m.n.0]-bicyclic ketones **318**, **319** and **320**, as in cyclohexanone since the trajectory of attack is the same. The presence of the bridging carbon inhibits path *a* somewhat in **321** and to a greater extent in **322**. There is also a preference for path *a* in complex compounds such as 3-cholestanone (**323**). Coprostanone (**324**) is an isomer of **323** and it also gives axial attack as shown (via path *a*) although the conformation of the molecule is slightly different.³¹⁵ The major diastereomeric product in bicyclic and polycyclic systems can be predicted with little or no modification of the simple cyclohexanone and cyclopentanone models presented above.



Table 4.11. Selectivity in Hydride Reduction of Bicyclic Ketones

MOLECULAR MODELING: Stereoselectivity of Nucleophilic Additions of Polycyclic Ketones

Reduction of bicyclic and polycyclic ketones is similar to that of monocyclic ketones, in that the reducing agent will approach the carbonyl "over" or "under" the ring, and will be subject to steric hindrance imposed by substituents on the ring. Bicyclic, tricyclic and polycyclic ketones such as A-F are generally more rigid that monocyclic ketones, however. Lithium aluminum hydride reduction of *trans*-2-decalone (A) occurs primarily from the *axial* face even though this appears to be more crowded than the *equatorial* face. This contrasts with the lack of stereoselectivity generally seen in reactions of unsubstituted steroidal ketones such as F. (Remember that the angle

^{315.} Reference 231, pp 127-129 and references cited therein.

MOLECULAR MODELING: Stereoselectivity of Nucleophilic Additions of Polycyclic Ketones, con't.

of approach for these and all other compounds considered here is (*a*) or (*b*) as shown for **A** rather than (*c*) or (*d*).) At what point in moving from **A** to **F** does the stereochemical preference diminish? To decide, examine LUMO maps for these and four "intermediate" structures, **B**–**E**.



First, examine the map for *trans*-2-decalone (A). By convention, regions where the LUMO is concentrated are colored "blue", while regions where it is absent are colored "red". The more blue the region, the more facile will be the reaction with the reducing agent. At which carbonyl face of A, *equatorial* or *axial*, is the LUMO more exposed? Next, compare the LUMO map for *trans*-2-decalone with those of the remaining structures, **B**–**F**. Are any changes observed, either in the preferred face of nucleophilic or in the magnitude of the preference? If there are, identify the structure at which these changes occur.

4.7.F. Selectivity in the Reduction of Natural Products

There are many synthetic examples where hydride reduction proceeds with high diastereoselectivity. Reduction of **325A** to alcohol **326** with lithium tri-*tert*-butoxyaluminum hydride is taken from Donaldson and Greer's synthesis of the C_3 - C_{15} bis(oxane) segment of phorboxazole.³¹⁶ The conformational drawing (**325B**) suggests that path *a* is preferred in the more stable chair conformation with the two substituents in the equatorial position. This model predicts the major alcohol product, which was converted as the acetate.



Another example involves a selective reduction of an acyclic ketone, albeit one that has a proximal dioxolane ring. Reduction of **327A** gave **328** in 96% yield with L-Selectride, in Prasad and Gholap's synthesis of (+)7-*epi*-goniofufurone.³¹⁷ The 3D model (**327B**) shows the

^{316.} Greer, P.B.; Donaldson, W.A. Tetrahedron Lett. 2000, 41, 3801.

^{317.} Prasad, K.R.; Gholap, S.L. J. Org. Chem. 2007, 72, 2.

large substituent is largely out-of-the way for path *a* or path *b*. The conformation of the sevenmembered ring, however, leads to some hindrance for path a, making path *b* preferred. This result is consistent with the stereochemistry of the final product, *syn*-diastereomer **328**. Note that the substituent is positioned in a such a way that a "pocket" is available for delivery via path *b*.



Reduction of norbornane-like precursors to natural products is also predictable. Reduction of the ketone unit in **329**, in Money and co-worker's synthesis of β -santalene for example, gave the exo-alcohol **330** via attack from the less hindered endo face.³¹⁸ Conversely, removal of the steric encumbrance at C7 in **331** gave attack via the exo face to give **332** (in about a 4:1 ratio favoring the endo alcohol shown).³¹⁹



There are many more examples of selectivity in reduction. These few illustrate that the simple principles discussed in this section, and the models used, can be applied to more complex systems with reasonable success.

MOLECULAR MODELING: Stereochemistry of Reduction of Spirocyclic Ketone

Sodium borohydride reduction of the spirocyclic ketone shown below gives a 13:1 mixture of two alcohols [De Shong et. al. J. Org. Chem. 1991, 56, 3207].



It is reasonable to expect that a LUMO map will be able to anticipate the direction of "hydride" attack (and hence the stereochemistry of the resulting alcohol). Remember that the nucleophile will be delivered to the carbonyl carbon either over or under the ring, based on the Bürgi-Dunitz trajectory. Before it can be used, however, it is first necessary to establish the conformation of the ketone. Assuming that both rings are chairs, there are four possible conformers, as shown, corresponding to whether the C–O bond in the ring that does not contain the carbonyl group is *equatorial* or *axial*. Build and obtain the energy for each of these. For each in turn,

^{318.} Hodgson, G.L.; MacSweeney, D.F.; Mills, R.W.; Money, T. J. Chem. Soc. Chem. Commun. 1973, 235.

 ⁽a) Benjamin, B.M.; Collins, C.J. J. Am. Chem. Soc. 1966, 88, 1556; (b) Kleinfelter, D.C.; Dye, T.E. Ibid. 1966, 88, 3174; (c) Kleinfelter, D.C.; Dye, T.E.; Mallory, J.E.; Trent, E.S. J. Org. Chem. 1967, 32, 1734.

MOLECULAR MODELING: Stereochemistry of Reduction of Spirocyclic Ketone, con't.

click on > to the right of the rightmost tab at the top of screen and *click* on *Continue* from list of buttons. Is one conformer significantly (>10 kJ/mol) more stable than any of the other three? If so, which conformer? Are both ring oxygen atoms *equatorial*, both *axial* or is one *equatorial* and the other *axial*? Attempt to rationalize your result. (Hint: consider the *anomeric effect* familiar in carbohydrate chemistry.)



Return to the screen that opened this problem by *clicking* on the leftmost tab at the top of the screen. Examine the LUMO map of the conformer that you have assigned as the lowest energy conformer, and identify on the face of the carbonyl group the LUMO is more concentrated. By convention, regions of maximum LUMO concentration are colored "blue" and regions of minimum concentration are colored "red", so you are looking for where the map is most blue. The maps are presented as transparent models allowing you to see the underlying structure. Once you identified the proper conformer and have oriented the model, you can switch to a solid model to better assess differences in the map for the two faces of the carbonyl group. First *click* on the map and then select *Solid* from the **Style** menu at the bottom of the screen. Does sodium borohydride reduction from the "preferred" face of the lowest energy conformer lead to the observed product?

4.8. CATALYTIC HYDROGENATION

Table 4.12.³²⁰ Typical hydrogenation catalysts.

Platinum oxide ^a	Platinum black ^b	Pt/C ^{c,b}	Pt/Rh oxided	Pd oxide ^e	Pd/BaCO3 ^f
Pd/SrCO3 ^g	Pd/C ^f	Rh/C ^f	Pd hydroxide/C ^h	Ni boride-P1 ⁱ	Ni(R) W3 ^q
Ni boride-P2 ^j	Ni (NiC) ^k	Ni-Kieselguhr ^m	Urushibara Ni ⁿ	Ni(R) W1 ^p	Ni-Cu ^l
Raney Ni [Ni(R)] ^o	Ni(R) W2 ^f	Copper chromite ^v	Ni(R) W4346 ^a	Ni(R) W8 ^t	Ni(R) W5 ^t
Ni(R) W6 ^s	Raney cobalt ^u	Ni(R) W7 ^r			

^{320.} See Reference 323, p 10.

a Ref.³²¹ b Ref.³²² c Ref.³²³ d Ref.³²⁴ e Ref.³²⁵ f Ref.³²⁶ g Ref.³²⁷ h Ref.³²⁸ i Ref.³²⁹ j Ref.³³⁰ k Ref.³³¹ l Ref.³³² m Ref.³³³ n Ref.³³⁴ o Ref.³³⁵ p Ref.³³⁶ q Ref.³³⁷ r Ref.³³⁸ s Ref.³³⁹ t Ref.³⁴⁰ u Ref.³⁴¹ v Ref.³⁴²

Reduction of functional groups with hydrogen gas is a key reaction in organic chemistry, dating to the first hydrogenation of ethene to ethane by von Wilde in 1874.³⁴³ As stated by Hudlicky',⁷ "true widespread use of catalytic hydrogenation did not start until 1897 when Sabatier and his co-worker developed the reaction between hydrogen and organic compounds to be a universal reduction method (Nobel Prize, 1912)."^{344,345} Other monographs that describe synthetic applications of catalytic hydrogenation are available from Rylander³⁴⁶ and from

- 321. (a) Adams, R.; Shriner, R.L. J. Am. Chem. Soc. 1923, 45, 2171; (b) Carothers, W.H.; Adams, R. Ibid. 1923, 45, 1071; (c) Keenan, C.W.; Giesemann, B.W.; Smith, H.A. Ibid. 1954, 76, 229; (d) Frampton, V.L.; Edwards, Jr., J.D.; Henze, H.R. Ibid. 1951, 73, 4432.
- (a) Willstätter, R.; Waldschmidt-Leitz, E. *Berichte* 1921, 54, 113 (see p121); (b) Baltzly, R. J. Am. Chem. Soc. 1952, 74, 4586; (c) Theilacker, W.; Drössler, H.G. Chem. Ber. 1954, 87, 1676.
- 323. Baltzly, R. J. Org. Chem. 1976, 41, 920.
- 324. (a) Nishimura, S. Bull. Chem. Soc. Jpn. 1961, 34, 32; (b) Idem, Ibid. 1960, 33, 566; (c) Idem Ibid. 1961, 34, 1544.
- 325. (a) Shriner, R.L.; Adams, R. J. Am. Chem. Soc. 1924, 46, 1683; (b) Starr, D.; Hixon, R.M. Org. Synth. Coll. Vol. 2 1943, 566.
- 326. Mozingo, R. Org. Synth. Collect. Vol. 3 1955, 181.
- Johnson, W.S.; Rogier, E.R.; Szmuszkovicz, J.; Hadler, H.I.; Ackerman, J.; Bhattacharyya, B.K.; Bloom, B.M.; (b)Stalmann, L.; Clement, R.A.; Bannister, B.; Wynberg, H. J. Am. Chem. Soc. 1956, 78, 6289.
- 328. Pearlman, W.M. Tetrahedron Lett. 1967, 1663.
- 329. Brown, C.A. J. Org. Chem. 1970, 35, 1900.
- (a) Brown, C.A.; Ahuja, V.K. J. Chem. Soc. Chem. Commun. 1973, 553; (b) Brown, H.C.; Sivasankaran, K.; Brown, C.A. J. Org. Chem. 1963, 28, 214; (c) Brubaker, Jr., C.H. in Catalysis in Organic Syntheses, 1977, Smith, G.W. (Ed.), Academic Press, New York, 1977.
- 331. Brunet, J.J.; Gallois, P.; Caubere, P. Tetrahedron Lett. 1977, 3955.
- 332. Takai, E. Sci. Pap. Inst. Phys. Chem. Res. 1968, 62, 24 [Chem. Abstr. 69: 30510h, 1968].
- 333. Covert, L.W.; Connor, R.; Adkins, H. J. Am. Chem. Soc. 1932, 54, 1651.
- (a) Taira, S. Bull. Chem. Soc. Jpn. 1961, 34, 1294; (b) Urushibara, Y. Ann. N.Y. Acad. Sci. 1967, 145, 52
 [Chem. Abstr. 68: 72708p 1968]; (c) Motoyama, I. Bull. Chem. Soc. Jpn. 1960, 33, 232.
- 335. (a) Pavlic, A.A.; Adkins, H.J. Am. Chem. Soc. 1946, 68, 1471; (b) Mozingo, R. Org. Synth. Coll. Vol. 31955, 181.
- 336. Covert, L.W.; Adkins, H. J. Am. Chem. Soc. 1932, 54, 4116.
- 337. Adkins, H.; Pavlic, A.A. J. Am. Chem. Soc. 1947, 69, 3039.
- 338. Adkins, H.; Billica, H.R. J. Am. Chem. Soc. 1948, 70, 695.
- 339. Billica, H.R.; Adkins, H. Org. Synth. Collect. Vol. 3 1955, 176.
- 340. Khan, N.A. J. Am. Chem. Soc. 1952, 74, 3018.
- 341. Reeve, W.; Eareckson II, W.M. J. Am. Chem. Soc. 1950, 72, 3299.
- 342. (a) Connor, R.; Folkers, K.; Adkins, H. J. Am. Chem. Soc. 1932, 54, 1138; (b) Adkins, H. Reactions of Hydrogen, University of Wisconsin Press, Madison, 1957.
- 343. von Wilde, M.P. Deutsch. Chem. Ber. 1874, 7, 352.
- 344. Reference 7, p 3.
- 345. Sabatier, P.; Senderens, J.B. Compt. Rend. 1897, 124, 1358.
- 346. Rylander, P.N. Catalytic Hydrogenation in Organic Synthesis Academic Press, New York 1979.

Freifelder,³⁴⁷ Applications of catalytic hydrogenation to organic chemistry are found in the series *Catalysis in Organic Reactions*.³⁴⁸ Catalytic hydrogenation is used to reduce alkenes,³⁴⁹ alkynes,³⁵⁰ ketones and aldehydes,³⁵¹ nitriles,³⁵² nitro compounds³⁵³ or aromatic rings.³⁵⁴

4.8.A. Catalytic Activity and Reactivity

Hydrogen gas is added to an organic molecule in the presence of a catalytic amount of a transition metal (see Table 4.12) and the reaction proceeds by adsorption of hydrogen and the substrate on the surface of the metal. The mechanistic rationale for this type of reduction will be discussed in Section 4.8.B. There are two major types of catalysis: **heterogeneous** (catalyst insoluble in the reaction medium) and **homogeneous** (catalyst soluble in the reaction medium). Catalytic heterogeneous hydrogenation can be **supported** (slurry and fixed gel operations)³²³ or **unsupported** (primarily solution reactions). The nature and amount of the catalyst and hydrogenation procedure employed influence which functional group that is reduced, the extent of reduction, and the product distribution. Laboratory scale reductions of organic functional groups containing a π bond usually involve a slurry process and an heterogeneous catalysis or homogeneous catalysis. Birch and Williamson reviewed homogeneous hydrogenation in synthesis.³⁵⁵

The most commonly used heterogeneous catalysts are platinum, palladium, nickel, rhodium, nickel, and ruthenium. Rylander gave references for the preparation of the most common catalysts, shown in Table 4.12.³³² In some cases, salts of transition metals are used rather than the metal itself although the pure metal adsorbed on a support (see above) is also commonly used. Hudlicky' presented an order of relative reactivity with propene for groups 8-10 transition metal catalysts, ³⁵⁶ based on the work of Mann and Lien.³⁵⁷

- 349. See Reference 17, p 7.
- 350. See Reference 17, p 28.
- 351. See Reference 17, p 1075.
- 352. See Reference 17, p 875.
- 353. See Reference 17, p 821.
- 354. See Reference 17, p 6.
- 355. Birch, A.J.; Williamson, D.H. Org. React. 1976, 24, 1.
- 356. Reference 7, p 4.
- 357. Mann, R.S.; Lien, T.R. J. Catal. 1969, 15, 1.

^{347.} Freifelder, M. Catalytic Hydrogenation in Organic Synthesis: Procedures and Commentary, Wiley, New York, 1978.

 ⁽a) Catalysis of Organic Reactions, Moser, W.R.; Marcel Dekker, New York, 1981; (b) Characterization of Heterogeneous Catalysts, Delannay, F. (Ed.), Marcel Dekker, New York, 1984; (c) Catalysis of Organic Reactions, Kosak, J.R. (Ed.), Marcel Dekker, New York, 1984; (d) Catalysis of Organic Reactions, Augustine, R.L. (Ed.), Marcel Dekker, New York, 1985; (e) Catalysis of Organic Reactions, Rylander, P.N.; Greenfield, H.; Augustine, R.L. (Ed.), Marcel Dekker, New York, 1988.

In this series, rhodium is the most active catalyst. The activation energy for the reaction of hydrogen with propene is also shown, and it is noteworthy that the catalytic activity does not correlate with the activation energy for the hydrogenation reaction (numbers below the metal). These catalysts are used for the hydrogenation of many functional groups, and Table 4.13^{358} correlates functional groups with recommended reaction conditions and catalysts. No single catalyst gives excellent results for all functional groups, and there are significant differences in chemo- and stereoselectivity. Note that most hydrogenations are done at ambient temperature and pressure. Only a few of the catalysts listed in Table 4.13 require high pressures, and then only for selected functional groups. In most cases, < 10 mol% of the catalyst is required per mole of the catalyst. The purpose of this table is to provide a quick guide to the reduction of common functional groups and to show the most common catalysts used. This section will focus on these catalysts and the functional groups they reduce.

Functional Group	Product	<u>Catalyst</u>	<u>mol %</u>	<u>Temp. (°C)</u>	Pressure (atm)
Alkene	Alkane	А	5-10	25	1-3
		В	0.5-3	25	1-3
		С	30-200	25	1-3
Alkyne	Alkene	D	8	25	1
		E	2 + 2% quinoline	20	1
		F	10 + 4% quinoline	25	1
	Alkane	в	3	25	1
Carboxylic Acid		С	20	25	1-4
Aromtic	Hydroaromatic	в	6-20 + AcOH	25	1-3
		G	40-60	25	1-3
	TT T	С	10	75-100	70-100
Heteroaromatic	Hydroaromatic	в	4-7 +AcOH or HCl/MeOH	25	1-4
		Н	20 + HCl/MeOH	65-200	130
		С	2	25	1
Aldehyde, Ketone	Alcohol	В	2-4	25	1-4
		Α	3-5	25	1
	I I. duo oo ah oo	Ç	30-100	25	1
Halide	Hydrocarbon	A	1-15 + KOH	25	1
		E	30-100 + KOH	25	1
		С	10-20 + KOH	25	1
RNO ₂ , Azide	Amine	в	1-5	25	1
		Α	4-8	25	1
		С	10-80	25	1-3
Oxime, Nitrile	Amine	В	1-10 + AcOH or HCl/MeOH	25	1-3
		А	5-15 + AcOH	25	1-3
		С	3-30	25	35-70
$A = 5\% Pd(C); B = PtO_2$ Reproduced with permiss	; C = Raney Ni; D	C =0.3% Pd(Cat	5-50 CO ₃); E = 5% Pd(BaSO ₄); F = Lindla <i>Chemistrv</i> by M. Hudlicky published	25 r catalyst; G = 5% in 1984 by Ellis F	35-70 Rh(Al ₂ O ₃); H =

Table 4.13.	Recommended Reaction Conditions for Catalytic Hydrogenation of Selected
Functional	Groups

^{358.} Reference 7, p 6.

In the context of hydrogenation, the **support** is an inert material on which the catalyst is adsorbed or admixed. Common supports are carbon (platinum black and palladium on carbon, for example) and alumina (rhodium is often adsorbed on alumina) and both calcium sulfate (CaSO₄) and barium sulfate (BaSO₄) are used. In part, the support dilutes the expensive transition metal catalyst, which allows one to control the rate of reaction as well as making it cost effective. Typically 1-10 mol % of the catalyst (see Table 4.13) is added to the support (sometimes called a carrier). The support can diminish the reactivity of the catalyst. Many other factors influence the reduction. These include the tendency of the catalyst to agglomerate, addition of a promoting substance, synergism between two catalysts, the temperature of the reaction, the ratio of hydrogen to compound being reduced, the pressure of hydrogen gas, the preparation method, the age of the catalyst, and the number of times it has been recycled.^{323,7,324}

For many applications, too active a catalyst will lead to overreduction and/or poor selectivity. If the activity of the metal catalyst is too high, addition of compounds that bind to the metal will usually diminish the activity by displacement of hydrogen atoms or the organic substrate being reduced. This process is referred to as **poisoning** of the catalyst, and it can greatly diminish the reducing power of that catalyst. In essence, when the poison is bound to the catalyst, hydrogen and the organic substrate cannot be bound, hence diminished reactivity. Common poisons include metal cations, halides, Hg^o, divalent sulfur compounds, carbon dioxide, amines and phosphines.³⁵⁹ In many cases, the organic molecule being reduced or a minor reaction product can poison the catalyst.³⁶⁰

A hydrogenation reaction is rather complex. The surface of the metal catalyst is very porous, allowing adsorption of hydrogen gas, organic substrates and various poisons. As the number of **active sites** (regions of the catalyst that can accommodate and bind hydrogen atoms and/ or organic substrates) increases, the rate of hydrogenation increases. A poison will bind to the active site in preference to the substrate or hydrogen, preventing their adsorption.³⁶¹ Gases such as carbon dioxide (CO₂) and carbon monoxide (CO) can fill up the active sites as well. Measurement of active sites in a catalyst is difficult. The position of the metal at the surface or just below the surface has a major influence on chemisorption. In many cases, metal salts are used as catalysts and a change in oxidation state during the reaction can deactivate the catalyst.³⁶¹

Reduction of alkenes with homogeneous catalysts will be presented in Section 4.8.B.

^{359. (}a) Reference 323, p 4; (b) Maxted, E.B. Adv. Catal. 1951, 2, 129; (c) Baltzly, R. J. Org. Chem. 1976, 41, 920, 928, 933.

^{360.} Smutny, E.J.; Caserio, M.C.; Roberts, J.D. J. Am. Chem. Soc. 1960, 82, 1793.

^{361.} Farranto, R.J.; Hobson, M.C.; Brungard, N.L. in Reference 325e, pp 177-209.



Figure 4.1. The principal surface and particle sites for heterogeneous catalysts. [Reproduced with permission from Maier, W.F. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 135. Copyright 1989 VCH Weinheim.]

Heterogeneous catalysis is a surface phenomenon, and it is known that there are different types of metal particles on the surface. Maier suggested the presence of terrace-, step- and kinktype atoms (in Fig. 4.1)³⁶² on the surface of a heterogeneous catalyst. These terms refer to different atom types characterized by the number of nearest neighbors,³⁶² which correspond to different transition metal fragments as well as to different coordination states of that metal.³⁶³ A terrace type atom (A in Fig. 4.1) typically has eight or nine neighbors and corresponds to a coordination model such as ML₅. The step type of atom (B) usually has seven neighbors and can be correlated with coordination model ML₄. Finally, the kink type atom (C) has six neighbors and corresponds to coordination model ML_3 . As the number and type of neighboring atoms around each type of atom changes, the binding capacity (active sites) will change. In general, as the particle size increases the relative concentration of terrace atoms will increase, whereas small particle size favors the kink type of surface atoms. Since the terrace atoms correspond to ML₅ transition metals, the step to ML₄ and the kink to ML₃ they should exhibit distinctly different reactivity.³⁶² Other factors can influence the way each type of atom will interact with an organic substrate, but it is clear the surface of the catalyst is important. Indeed, Maier suggested that the ideal catalyst would be "a material with the right surface structure rather than an empirical mixture of ingredients".³⁶³ It is likely that the use of modifiers, poisons, and special reaction conditions will change the shape, size, and surface structure of the catalyst. This will, of course, influence the selectivity and reactivity. With palladium, both "hydrogenation and hydrogenolysis were found to be sensitive to the surface structure and morphology of the catalyst."362 It is important to emphasize that Maier states he does not believe this analysis applies to homogeneous catalysis.³⁶³ There are several interesting differences between homogeneous and heterogeneous catalysis. The soluble homogeneous catalysts usually have a dissociated ligand and/or a coordinating solvent that will compete with the organic substrate for active metal sites. Heterogeneous catalysts behave essentially as an insoluble matrix, whereas the homogeneous catalyst is soluble in the reaction solvent and functions as a discreet molecule. Because heterogeneous catalysts are insoluble, only those metal atoms at the surface of the matrix are thought to be important for hydrogenation as noted above. Much of the catalyst is

^{362.} Maier, W.F. Angew. Chem. Int. Ed. 1989, 28, 135.

^{363.} Maier, W.F. in Reference 325e, pp 211-231, Cf. p 220.

within the matrix and inaccessible. The soluble homogeneous catalyst allows each molecule of catalyst to be accessible (sec. 4.8.B). Thus, homogeneous reactions require less catalyst. The matrix nature of heterogeneous catalysts often means poor chemoselectivity, bond migration, hydrogenolysis and so on (see below). Prediction of stereochemistry in the final product is usually difficult because chemisorption is required for reaction, and the precise nature of the chemisorption is difficult to ascertain. Since heterogeneous catalysts often require polar solvents, problems can arise due to the poor solubility of hydrogen gas in the solvent. The large surface area of heterogeneous catalysts make them susceptible to poisoning, as discussed above, but homogeneous catalysts are soluble and many of the problems arising from chemisorption at a surface disappear. Homogeneous catalysts tend to be significantly more selective for alkenes and alkynes, show less reactivity with heteroatom-containing functional groups, and they are less prone to poisoning.³³² Nonpolar solvents (such as benzene, and methylene chloride) can be used with homogeneous catalysts, which is important because such solvents can dissolve more hydrogen gas, facilitating the reduction. Reaction with an organic substrate occurs with more or less discreet catalyst molecules of known coordination states. The stereochemistry of the reduction product is often predictable by analysis of the geometry of substrate binding around the metal (the binding of hydrogen, solvent and other ligands must also be known). Typical homogeneous catalysts include Wilkinson's catalyst (Ph₃P)₃RhCl (336)³⁶⁴ and the iridium complex $[Ir(cod)(Py)PCy_3]^+ PF_6^-$, which is related to Vaska's catalyst (see 341).³⁶⁵ It is also clear that the main difference between an homogeneous and heterogeneous catalyst is the presence of an organic substrate called a ligand [pyridine (Py), cyclooctadiene (COD), tricyclohexylphosphine (PCy₃), triphenylphosphine, bis(phosphine) ligands, and mono and diamines] in the homogeneous catalyst. These ligands bind to the metal whereas heterogeneous catalysts typically consist of transition metals (M°), metal halides or metal oxide salts MX₂, MX_4 , and so on where X is Cl or O.

4.8.B. Hydrogenation of Alkenes

Catalytic hydrogenation is commonly used for the reduction of alkenes, alkynes, aromatic hydrocarbons, and aromatic heterocycles, carbonyl derivatives, nitriles or nitro compounds. The reaction with alkenes proceeds on the surface of a heterogeneous metal catalyst, via cleavage of diatomic hydrogen and adsorption of the hydrogen atoms. Horiuti and Polanyi proposed a mechanism in 1934 for the reduction of ethene with hydrogen on nickel.³⁶⁶ In each step, (*) referred to an undefined nickel atom or complex. It was proposed that hydrogen gas was cleaved to hydrogen atoms that were bound to the nickel (represented by **333**). An

^{364. (}a) Jardine, F.H., Osborn, J.A.; Wilkinson, G.; Young, G.F. Chem. Ind. (London) 1965, 560; (b) Imperial Chem. Ind. Ltd., Neth. Appl. 6,602,062 [Chem. Abstr. 66: 10556y 1967]; (c) Bennett, M.A.; Longstaff, P.A. Chem. Ind., 1965, 846; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 868-869.

^{365.} Suggs, J.W.; Cox, S.D.; Crabtree, R.H.; Quick, J.M. Tetrahedron Lett. 1981, 22, 303.

^{366.} Horiuchi, J.; Polányi, M. Trans. Faraday Soc. 1934, 30, 1164.

alkene was also bound to the surface of the metal (represented by **334**), allowing the reaction to proceed, with transfer of hydrogen to the carbon (in **335**). This model is misleading, since the surface is porous and may contain metal atoms in more than one coordination state for heterogeneous catalysts (see above). The exact mechanism of heterogeneous catalysis is not well understood since it is a surface phenomenon. It is clear that the catalyst ruptures the H-H bond to generate a metal-H (H*) species where hydrogen is adsorbed at an active site on the surface of the catalyst. The differing ability of metals to bind hydrogen and to transfer that hydrogen to an organic substrate is a critical factor that leads to differences in reduction for different catalysts.



Hydrogen adsorption is best understood for the reduction of alkenes with homogeneous catalysts, because the hydrogenation involves discreet, well-defined particles. Wilkinson's catalyst [**336**, (Ph₃P)₃RhCl] has been studied extensively. Wilkinson's catalyst is prepared from rhodium chloride (RhCl₃) and triphenylphosphine in ethanol (88% is a typical yield of **336**).³⁶⁷ The mechanism of activation when used for hydrogenation of alkenes is hydrogen activation, substrate activation, and hydrogen transfer.³⁶⁸ A mechanistic picture of the reaction is shown for the reaction of the square planar catalyst (**336**) with hydrogen gas to form a trigonal bipyramidal species, **337**.³⁶⁹ Subsequent reaction with the alkene will replace a phosphine ligand to give a species such as **338**. It is also possible that the alkene binds to the catalyst first, followed by hydrogen. Hydrogen is transferred from rhodium to carbon in a stepwise manner, generating a species such as **339**. Release of the alkane generates a trigonal species (**340**) that reacts with additional hydrogen to regenerate **337**. Cotton and Wilkinson used this cycle to illustrate the hydrogenation of alkenes.³⁷⁰

^{367.} Osborn, J.A.; Jardine, F.H.; Young, J.F.; Wilkinson, G. J. Chem. Soc. A 1966, 1711.

^{368. (}a) Collman, J.P. Acc. Chem. Res. 1968, 1, 136; (b) Vaska, L. Ibid. 1968, 1, 335; (c) Halpern, J. Quart. Rev. 1956, 10, 463; (d) Idem, J. Phys. Chem. 1959, 63, 398; (e) Idem, Ann. Rev. Phys. Chem. 1965, 16, 103.

^{369.} Tolman, C.A.; Meakin, P.Z.; Lindner, D.L.; Jesson, J.P. J. Am. Chem. Soc. 1976, 96, 2762.

Cotton, F.A.; Wilkinson, G.; Murillo, C.A.; Bochmann, M. Advanced Inorganic Chemistry, 6th ed, Wiley, New York, 1999, p 1231.



[Reprinted in part with permission from Tolman, C.A.; Meakin, P.Z.; Lindner, D.L.; Jesson, J.P. J. Am. Chem. Soc. 1976, 96, 2762. Copyright © 1976 American Chemical Society.]

There are many other homogeneous catalysts, involving several different transition metals. **Vaska's catalyst (341)** is one of the more important and it also reacts with hydrogen, converting the square planar catalyst to the octahedral intermediate **342**.³⁷¹ Reduction of an alkene probably involves replacement of the triphenylphosphine ligand with hydrogen or an alkene in a reversible process.³³²



As shown above, the mechanism of hydrogenation involves coordination of the organic substrate to the metal, usually via π bonds or lone pairs of electrons on heteroatom functional groups. The ability to bind the substrate, how it is bound (π complex or metal-carbon bond) and its reactivity to metal-bound hydrogen are the other factors determining differences in catalysis. Rylander's book³²³ examines the reduction of many functional groups, and finds that palladium is preferred for reduction of alkenes, platinum for carbonyl, and rhodium for selective reduction of aromatic rings. The following order of reactivity is useful for general applications:

Pt	C=O	>>	C=C	>	(H)	>	Ar
Pd	C=C	>	(H)	>	C=O	>	Ar
Ru	C=O	>	C=C	>	Ar	>	(H)

where $(\mathbf{H}) =$ hydrogenolysis

With proper choice of catalyst, high chemoselectivity can be achieved. In the Hagiwara et al. synthesis of (*R*)-(+)-muscopyridine,³⁷² for example, hydrogenation of **343** with a Pd-C catalyst gave a 98% yield of diketone **344**, with no reduction of the ketone units. Alkenes can be

^{371.} Vaska, L.; Diluzio, J.W. J. Am. Chem. Soc. 1962, 84, 679.

^{372.} Hagiwara, H.; Katsumi, T.; Kamat, V.P.; Hoshi, T.; Suzuki, T.; Ando, M. J. Org. Chem. 2000, 65, 7231.

reduced in the presence of benzylic substituents without hydrogenation. In a synthesis of (-)-anaferine³⁷³ by Blechert and Stapper, both alkene units in **345** were hydrogenated to give **346** in 87% yield, without reduction of the benzyl units.



The phenomenon of *hydrogenolysis* (cleavage of a C–X bond, where X is an heteroatom) was introduced with the discussion of LiAlH₄ reduction and involves cleavage of carbonheteroatom bonds, although it did not occur in **345** since reduction of the C=C unit was more facile. This process is particularly facile when the C–X bond is allylic or benzylic to a π -bond. Reaction with hydrogen cleaves the C–X bond (see **347**) to give the hydrocarbon (**348**). The ability of a catalyst to effect hydrogenolysis is indicated by (H) in the comparison of catalyst reactivity for Pt, Pd and Ru. The group X can be halogen, alcohol, ether, amine, and so on. A synthetic example of hydrogenolysis is cleavage of the O-benzyl unit in **349** to give **350**, as part of Lee and co-worker's synthesis of SCH 351448, a novel activator of low-density lipoprotein receptor (LDL–R) promoter.³⁷⁴ As shown in this example, hydrogenolysis of the PhCH₂O–CH₂- unit leads to the alcohol and toluene (PhCH₂–H).



The order of catalytic ability shown above for platinum, palladium, and ruthenium is most useful when a catalyst must be chosen for hydrogenation of a multifunctional molecule. In molecules containing an alkene and a ketone or aldehyde, platinum catalysts selectively reduce the carbonyl. There are also differences in conjugated versus nonconjugated alkenes. An example of this selectivity is the reduction of **351** with palladium and strontium carbonate (SrCO₃), which gave selective reduction of one alkene unit to **352** without reducing either the conjugated carbonyl or the cyclopentanone moiety. Changing to a palladium-on-carbon

^{373.} Blechert, S.; Stapper, C. Eur. J. Org. Chem. 2002, 2855.

^{374.} Kang, E.J.; Cho, E.J.; Lee, Y.E.; Ji, M.K.; Shin, D.M.; Chung, Y.K.; Lee, E. J. Am. Chem. Soc. 2004, 126, 2680.

catalyst led to selective reduction of the conjugated double bond to give 353 in 87% yield.³⁷⁵



In general, more highly substituted alkenes do not adsorb on the catalyst as effectively and are not readily reduced, which implies that vinyl groups are easily reduced but tetrasubstituted alkenes are very sluggish. The relative order of reduction for mono, di-, tri- and tetrasubstituted alkenes is:



Unfortunately, this selectivity for reduction of the less hindered double bond is not always observed and varies considerably with the catalyst and reaction conditions (see Table 4.13).^{358,376} When a double bond is highly strained, it is more easily reduced.³⁷⁶



The reduction of the exo-methylene group in **354** to **355** illustrates this selectivity.³⁷⁷ The exocyclic methylene group is more strained than the internal double bond, which is part of the cyclopentene moiety. Selective reduction of the methylene unit was observed, although the methylene is only disubstituted and the cyclopentene unit is trisubstituted.

Isomerization of the double bond and even rearrangement are problems with some catalysts, and catalysts vary widely in their ability to induce isomerization. An order of ability to promote double bond migration was reported by Rylander, based on work by Gostunskaya et al.³⁷⁸

$$Pd > Ni >> Rh \approx Ru > Os \approx Ir > Pt$$

This relative order of bond migration is the same as the relative ability of these metals to absorb hydrogen gas. Rhodium does not show significant isomerization at low temperatures, but

- 377. Marx, J.N.; McGaughey, S.M. Tetrahedron 1972, 28, 3583.
- 378. (a) Reference 323, p 37; (b) Gostunskaya, I.V.; Petrova, V.S.; Leonova, A.I.; Mironova, V.A.; Abubaker, M.; Kazanskii, B.A. *Neftekhimiya* 1967, 7, 3 [*Chem. Abstr.* 67: 21276t, 1967].

^{375.} Daniewski, A.R.; Kabat, M.M.; Masnyk, M.; Wicha, J.; Wojciechowska, W.; Duddeck, H. J. Org. Chem. 1988, 53, 4855.

^{376.} Reference 323, p 34.

isomerization is facile at temperatures > 80° C.³⁷⁹ Reduction of car-3-ene (**356**) with a platinum catalyst gave carane (**357**), but using a palladium catalyst led to **360**. The initial reaction was a bond isomerization to give **358**, but subsequent opening of the cyclopropane ring gave **359**. The final product (**360**) was generated by reduction of the double bond in **359**.³⁸⁰



One way to explain the observed results in the reduction of **356** is that palladium binds alkenes reversibly, whereas platinum binds them more tightly and essentially irreversibly. If true, this has consequences for the stereochemistry (cis/trans-) of the final product. Banwell and coworker's synthesis of γ -lycorane involved reduction of **361** to **362**,³⁸¹ where the cis-relationship of the 6-5 ring juncture led to delivery of hydrogen selectively from the bottom of **361** to give the observed stereochemistry in **362**. This experiment suggests that binding hydrogen atoms and the alkene unit to palladium leads to delivery of both hydrogens from the same face.



Clean formation of predominantly one stereoisomer also suggests that the alkene is bound tightly to the metal. If the alkene isomerizes prior to delivery of hydrogen, or if the alkyl moiety is not bound tightly to the metal after the first hydrogen is delivered, the alkyl-metal intermediate will equilibrate *prior* to delivery of the second hydrogen. Such an event usually favors the trans-product or, in general, the thermodynamically more stable product. When either a cis- or a trans-product can be produced, catalysts differ significantly in their ability to give the cis-product. The ability of the catalyst to give primarily cis-products on hydrogenation is^{382,380}

Ir > Os > Pt,Ru,Rh >> Pd

Platinum is an excellent choice to give the cis adduct (the reduction is essentially under kinetic control) and palladium will usually give primarily the trans adduct (the reduction is essentially

^{379.} Bond, G.C.; Wells, P.B. Adv. Catal. 1964, 15, 91.

^{380. (}a) Reference 323, p 41; (b) Cocker, W.; Shannon, P.V.R.; Staniland, P.A. J. Chem. Soc. C 1966, 41.

^{381.} Banwell, M.G.; Harvey, J.E.; Hockless, D.C.R.; Wu, A.W. J. Org. Chem. 2000, 65, 4241.

^{382.} Nishimura, S.; Sakamoto, H.; Ozawa, T. Chem. Lett. 1973, 855.

under thermodynamic control). If the selectivity observed in the hydrogenation of **354** is examined more closely, one sees that the platinum probably does not isomerize the alkene prior to delivery of hydrogen nor lead to thermodynamic control. Face *b* is probably not the less hindered face for coordination to the catalyst. The oxygen atoms of the lactone ring may play a role, holding the catalyst and facilitating reduction from that face (a neighboring group effect, see the discussion of haptophilicity below). Note that if **354** gives a reduction product with high stereoselectivity, other molecules with similar structures may show the same stereochemistry. It *may* therefore be possible to predict the major product of hydrogenation reactions by examining the literature for reduction of alkenes with a similar structure. For all reductions, a thorough search of the literature for relevant examples is important.

Predicting the stereochemistry of reduction can be difficult in many cases, and identification of the less hindered face can also be difficult. Rylander pointed out that adsorption may occur to minimize steric interaction but that step may not control the stereochemistry of the final product. The example of **354** seems to reinforce this statement. Control of stereochemistry can vary with the degree of isomerization, the catalyst, reaction conditions, and the purity of the alkene.^{383,384} Norbornene systems usually give exclusively exo-(cis)-addition of hydrogen unless there is significant steric encumbrance at the C7 position.³⁸⁵

Another phenomenon that influences the stereochemistry of reduction in alkene systems is **haptophilicity**, an anchoring effect in which a functional group binds to the surface of the catalyst and directs delivery of hydrogen from that side of the molecule.³⁸⁶ This is analogous to the neighboring group effects encountered in previous sections and chapters. As with other neighboring group effects, the extent of its importance greatly depends on the hydrogenation solvent. Hydrogenations that used heterogeneous catalysts are usually explained in terms of "approach, fit and binding of the reducible molecule to the surface of the catalyst".^{386,387} This is especially true when the geometry of a molecule or substituent hinders approach or fit.³⁸⁸ The presence of a chelating group often produces stereochemistry opposite to that predicted by steric effects.³⁸⁹ Different modes for adsorption of a haptophile on the surface of a catalyst are illustrated in Figure 4.2.³⁷¹ Reduction of amine **363** illustrates haptophilicity. The aminomethyl group is bound to the catalyst³⁹⁰ and directs the hydrogen from the same face as the aminomethyl,

^{383.} Reference 323, p 43 and references cited therein.

^{384.} Siegel, S.; Cozort, J.R. J. Org. Chem. 1975, 40, 3594.

^{385. (}a) Baird, Jr., W.K.; Surridge, J.H. J. Org. Chem. 1972, 37, 1182; (b) Baird, Jr., W.C.; Franzus, B.; Surridge, J.H. Ibid. 1969, 34, 2944.

^{386. (}a) Reference 323, p 44; (b) Thompson, H.W.; Naipawer, R.E. J. Am. Chem. Soc. 1973, 95, 6379.

^{387. (}a) Burwell, Jr., R.L. Chem. Rev. 1957, 57, 895; (b) Siegel, S. Adv. Catal. 1966, 16, 123.

^{388. (}a) Hadler, H.I. Experientia 1955, 11, 175; (b) Hanaya, K. Bull. Chem. Soc. Jpn. 1970, 43, 442.

^{389.} Reference 386b, citations 10 and 6-9 therein.

^{390.} Thompson, H.W.; Wong, J.K. J. Org. Chem. 1985, 50, 4270 and references cited therein.

to give **364** with formation of only 10% of the syn diastereomer (**365**).³⁹¹



(a) Failure of adsorption cis to a hindering group(b) Adsorption trans to a hindering or haptophilic group(c) Adsorption cis to a haptophile

Figure 4.2. Adsorption of a haptophile on the surface of a catalyst. [Reprinted in part with permission from Thompson, H.W.; Naipawer, R.E. J. Am. Chem. Soc. 1973, 95, 6379. Copyright © 1973 American Chemical Society.]



The first mode illustrated in Figure 4.2³⁸⁶ suggests that a neighboring group can interfere with the haptophilic effect, presumably by preventing the required hydrogen bonding or dipole interaction. Hydrogenation of 3 β -substituted Δ^5 -steroids [such as 3 β -cholesteryl methyl ether (**366**)] yields the saturated derivative with a trans-A/B ring juncture (H is trans to the bridgehead methyl), in most cases.³⁹² Hydrogenation of 3 α -substituted steroids³⁹³ such as epicholesteryl methyl ether (**367**), however, gave a cis-A/B ring juncture. This latter reduction required the addition of catalytic amounts of perchloric or sulfuric acid and failed when done in ethanolic potassium hydroxide.³⁹⁴ The α -methoxy group prevented adsorption on the α face. Binding occurred on the β face, leading to a cis-A/B ring juncture (H is cis to the bridgehead methyl), illustrates case (a) in Figure 4.2.



The second and third binding modes shown in Figure 4.2 can be illustrated by the reduction of **368**. The ester group in **368** functions as a poor haptophile and does not bind very well to the metal. Steric hindrance leads to the alkene moiety binding to a catalyst particle from the

 ^{391. (}a) For other work involving stereocontrol in hydrogenation reactions, see Thompson, H.W.; McPherson, E. J. Am. Chem. Soc. 1974, 96, 6232; (b) Reference 323, p 45.

^{392.} Wagner-Jáuregg, T.; Werner, L. Z. Physiol. Chem. 1932, 213, 119.

^{393.} Shoppee, C.W.; Agashe, B.D.; Summers, G.H.R. J. Chem. Soc. 1957, 3107.

^{394.} Wilds, A.L.; Johnson, Jr., J.A.; Sutton, R.E. J. Am. Chem. Soc. 1950, 72, 5524.

opposite face, and the product (**369**) has the trans-stereochemistry for the ring juncture.^{393,386b} Hydrogenation was followed by lithium aluminum hydride reduction of **369** and gave **372**. If the order of reactions is reversed and **368** is first reduced with LiAlH₄ (to give **370**) and then subjected to catalytic hydrogenation, a haptophilic effect of the alcohol (see **373**) delivers hydrogen to that face, giving **371**. The presence of the hydroxymethyl group in **371** led to the opposite stereochemistry upon hydrogenation when compared to that observed with the ester group in **373**, illustrating the difference between the second and third cases in Figure 4.2.



4.8.C. Hydrogenation of Alkynes

Alkynes contain π bonds, of course, and catalytic hydrogenation is usually straightforward. There are two significant problems with hydrogenation of alkynes, however. Hydrogenation of the triple bond first gives an alkene, but overreduction can occur to give an alkane moiety (a two-stage reduction, sec. 4.1). Since the initial product is an alkene product, there is the possibility of stereochemical control problems during the course of the hydrogenation, and hydrogenation of alkynes generally produces a mixture of both cis and trans isomers.

Selective reduction to the alkene without overreduction requires that the alkyne be adsorbed to the catalyst more tightly than the alkene. To selectively generate a cis alkene also requires that double bond migration and cis-trans isomerization of the alkene product be minimized. Palladium is usually a poor choice since both of these processes are faster than transfer of a hydrogen atom to the alkene. An order has been established for selectivity in the reduction of 2-pentyne to 2-pentene³⁹⁵ without reduction of the C=C moiety in 2-pentene.

Pd > Pt > Ru > Rh > Ir

Selectivity for formation of the cis alkene (usually 91-98%) was

^{395. (}a) Bond, G.C.; Wells, P.B. J. Catal. 1966, 5, 419; (b) Reference 323, p 16.

$Pd > Rh > Pt > Ru \sim Ir$

The best reagent for selective reduction of alkynes to the cis alkene is the **Lindlar catalyst**.³⁹⁶ Palladium chloride (PdCl₂) was precipitated on calcium carbonate (CaCO₃) in acidic media and deactivated with lead tetraacetate [Pb(OAc)₄] to give the named Pd-CaCO₃-PbO catalyst. Reduction of alkynes will stop at the cis alkene with little or no cis-trans isomerization. A variation uses quinoline as a poison, illustrated in Koide and co-worker's synthesis of FR901464, in which alkyne **374** was converted to cis-alkene **375** in excellent yield.³⁹⁷ Cram and Allinger used a palladium on barium sulfate (BaSO₄) catalyst poisoned with quinoline^{398a} (sometimes called the **Rosenmund catalyst**),^{398b-d} to achieve the same selectivity. The poison is required to deactivate the catalyst (quinoline coordinates to the active sites on the metal), reducing the propensity for overreduction and bond migration. This Cram-Allinger catalyst is widely used in organic synthesis, and is commonly called a Lindlar catalyst. A mixture of nickel boride (Ni₂B) on borohydride exchange resin also gives cis alkenes upon hydrogenation of alkynes.³⁹⁹

AcO

$$O$$

 O
 $H_2, 10\%$ quinoline
 $H_2, 10\%$ quinoline
 $H_2, 3^{\circ}C$
 H_2
 H_2

Just as homogeneous catalysts were shown to give superior stereoselectivity with alkenes, relative to homogeneous catalysts,⁴⁰⁰ homogeneous catalysts can give improved selectivity with alkynes. This selectivity is illustrated in syntheses of (+)-blastmycinone and (–)-litsenolide C1, by Liu and co-workers⁴⁰¹ in which the hydrogenation of the conjugated alkyne unit **376** with Wilkinson's catalyst gave a 90% yield of **377**.⁴⁰² In this case, the selectivity was for the alkyne over the alkene, although the alkyne was completely reduced to the hydrogenolysis of a C-Br bond, as in the hydrogenation of ω -halo alkenes such as 6-bromo-1-hexene to 1-bromohexane in 78% yield.⁴⁰³

The en-yne unit in 376 was selectively reduced, and it is known that dienes are hydrogenated

- 399. Choi, J.; Yoon, N.M. Tetrahedron Lett. 1996, 37, 1057.
- 400. Milstein, D. Acc. Chem. Res. 1984, 17, 221.
- 401. Chen, M.-J.; Lo, C.-Y.; Chin, C.-C.; Liu, R.-S. J. Org. Chem. 2000, 65, 6362.
- 402. Evans, D.A.; Morrissey, M.M. J. Am. Chem. Soc. 1989, 106, 3866.
- 403. Januskiewicz, K.R.; Alper, H. Can. J. Chem. 1984, 62, 1031.

^{396. (}a) Reference 15, p 566; (b) Lindlar, H. Helv. Chim. Acta 1952, 35, 446.

^{397.} Albert, B. J.; Sivaramakrishnan, A.; Naka, T.; Koide, K. J. Am. Chem. Soc. 2006, 128, 2792.

^{398. (}a) Cram, D.J.; Allinger, N.L. J. Am. Chem. Soc. 1956, 78, 2518; (b) Rosenmund, K.W. Berichte 1918, 51, 585; (c) Mosettig, E.; Mozingo, R. Org. React. 1948, 4, 362; (d) Rachlin, A.I.; Gurien, H.; Wagner, D.P. Org. Synth. Coll. Vol. 6 1988, 1007.

to give alkenes, but over-reduction is a problem, as it was with alkynes. Homogenous catalysts can be of value. The diene unit in **378** was hydrogenated to give the non-conjugated alkene unit in **379** (80% yield) in the Serebryakov et al. synthesis of faranal.⁴⁰⁴ Both 1,2- and 1,4-reduction are possible, and the major product depends on the catalyst used, as well as the substituents on the C=C units of the diene.



It is possible to reduce cyclopropane rings by catalytic hydrogenation, using even a heterogeneous catalyst such as platinum oxide (PtO₂, often called the **Adams' catalyst**). Cyclopropane rings can react with active catalysts, opening during hydrogenation to generate a geminal dimethyl

group. In one example, **380** was reduced to **381** to complete Taber and co-worker's synthesis of *trans*-dihydroconfertifolin.⁴⁰⁵ The use of a platinum catalyst maximized the hydrogenolysis and minimized reduction of the carbonyl.



4.8.D. Hydrogenation of Carbonyl Compounds

The π bond of a carbonyl can be reduced by catalytic hydrogenation to give an alcohol. Problems of chemoselectivity and stereoselectivity are common with these compounds as they were with alkenes and alkynes. Hydrogen, in the presence of palladium catalysts, reduces alkenes faster than carbonyls and platinum is usually the preferred catalyst for carbonyls. This preference is apparent in the hydrogenation of **382** to (–)-muscone (**383**), in the final step in an asymmetric synthesis by Hagiwara and co-workers.⁴⁰⁶ With alkenyl aldehydes, platinum reduces the aldehyde preferentially when adsorbed on carbon or calcium carbonate, but not when adsorbed on barium sulfate or alumina (Al₂O₃).⁴⁰⁷ In general, catalytic hydrogenation of a ketone unit is straightforward. The proliferation of readily available, easy to use and highly selective hydride and borane reducing agents often makes catalytic hydrogenation a second choice for reducing heteroatom containing functional groups, particular carbonyl derivatives. Many heteroatom functional groups are compatible with hydrogenation of ketones, however.

^{404.} Vasil'ev, A.A.; Engman, L.; Serebryakov, E.P. J. Chem. Soc. Perkin Trans. 1 2000, 2211.

^{405.} Taber, D.F.; Nakajima, K.; Xu, M.; Rheinagold, A.L. J. Org. Chem. 2002, 67, 4501.

^{406.} Kamat, V.P.; Hagiwara, H.; Katsumi, T.; Hoshi, T.; Suzuki, T.; Ando, M. Tetrahedron 2000, 56, 4397.

^{407.} Reference 323, p 75.

In a synthesis of plumerinine, Comins and co-workers reduced the ketone unit in **384** to give alcohol **385** in 96% yield using platinum oxide (**Adams' catalyst**).⁴⁰⁸



Hydrogenation of conjugated carbonyl compounds can give either 1,2- or 1,4-reduction or a mixture, but changing the catalyst usually controls the product distribution. The palladium-

catalyzed hydrogenation of **386**, for example, cleanly reduced the alkene unit to give **387** in 96% yield.⁴⁰⁹ Hydrogenation of similar compounds using a platinum catalyst generally leads to preferential reduction of the carbonyl unit.



Hydrogenolysis (reductive cleavage) of the C-O bond is rarely a problem in aliphatic carbonyl compounds, and new catalysts⁴¹⁰ are being developed all the time. The presence of an heteroatom substituent may lead to significant hydrogenolysis, however, as in the reduction of the ester ethyl 3-oxobutanoate (**388**).⁴¹¹ Reduction gave the expected alcohol product (ethyl 3-hydroxybutanoate, **389**), but hydrogenolysis of the C-O bond in **389** gave ethyl butanoate as a side product. It is important to note, however, that it is possible the alcohol moiety in **389** eliminated under the reaction conditions and the resultant alkene moiety was further reduced. Hydrogenolysis *may* not be involved in this transformation at all, but the cited reference suggested that it probably was. In the case of **388**, platinum black gave the greatest amount of reductive cleavage (90% ethyl butanoate and 10% of **389**). The use of additives and of platinum oxide (100% **389**) led to reduction of the ketone without hydrogenolysis.



When the carbonyl of ketones or aldehydes is conjugated to aromatic systems, hydrogenolysis products are often the major isolated products. Catalytic hydrogenation of 2-naphthaldehyde (**390**) with palladium-on-barium sulfate gave only 2-methylnaphthalene (**391**).⁴¹² When the **Adams'** catalyst (PtO₂) was used, with ferric chloride (FeCl₃) as a promoter, an 80% yield of alcohol **392** was obtained, although addition of excess promoter induced further hydrogenolysis to **391**.

^{408.} Comins, D.L.; Zheng, X.; Goehring, R.R. Org. Lett. 2002, 4, 1611.

^{409.} Tudanca, P.L.L.; Jones, K.; Brownbridge, P. J. Chem. Soc. Perkin Trans. 1 1992, 533.

^{410.} See, for example, Ohkuma, T.; Ooka, H.; Yamakawa, M.; Ikariya, T.; Noyori, R. J. Org. Chem. 1996, 61, 4872.

^{411.} Reference 323, p 86.

^{412.} Campbell, N.; Anderson, W.; Gilmore, J. J. Chem. Soc. 1940, 819.



Hydrogenolysis was also observed in the reduction of 2-acetylthiophene (**393**), when the homogeneous catalyst cobalt octacarbonyl $[Co_2(CO)_8]$ was used, and 2-ethylthiophene (**394**) was isolated in 52% yield.⁴¹³ The homogeneous catalyst was necessary to minimize poisoning by the sulfur compound. As mentioned earlier, homogeneous catalysts are usually less susceptible to poisoning.⁴¹⁴ In general, reduction to the alcohol is rapid with aromatic aldehydes using palladium, but slow with ruthenium. The reverse is observed with aliphatic aldehydes. Hydrogenolysis can occur in acidic media, or with vigorous reaction conditions. Catalysts are available, however, that allow hydrogenation of a ketone unit that is attached to a heterocyclic ring, giving the alcohol without significant hydrogenolysis. An example is a homogeneous ruthenium catalyst used to hydrogenate **395** to **396** in 96% yield, and with high enantioselectivity (see below).⁴¹⁵



Some acid derivatives are reduced by catalytic hydrogenation. Relative to alkenes and ketones, several acid derivatives were seen to be less reactive in previous examples. There is a clear difference in reactivity, apart from specificity for the metal catalyst. The ability of hydrogen to reduce acid derivatives follows the expected order, and acid chlorides will be reduced faster than esters, for example. Aldehydes and ketones⁴¹⁶ are reduced significantly faster than all acid derivatives except acid chlorides. The general order of reactivity for hydrogenation is

$$\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 0 \\ R \stackrel{\checkmark}{\longrightarrow} Cl > R \stackrel{\checkmark}{\longrightarrow} H(R) > R \stackrel{\checkmark}{\longrightarrow} O \stackrel{\land}{\longrightarrow} R > R \stackrel{\checkmark}{\longrightarrow} OR > R \stackrel{\land}{\longrightarrow} OH > R \stackrel{\land}{\longrightarrow} NH_2$$

Esters are difficult to reduce by hydrogenation and the reduction of alkenes, alkynes, aldehydes or ketones in the presence of esters and amides is usually facile. Hydrogenation of carboxylic acids is very difficult. The use of ruthenium oxide (RuO_2) or ruthenium on carbon (Ru/C), at high pressure and temperatures, is a preferred method for reduction of acids to alcohols. Hydrogenolysis can be a problem with esters possessing an allylic or benzylic C–O bond, as in

^{413.} Greenfield, H.; Metlin, S.; Orchin, M.; Wender, I. J. Org. Chem. 1958, 23, 1054.

^{414. (}a) Marko, L. Proc. Sympos. Coord. Chem. Tihany Hung. 1964, 271 [Chem. Abstr. 65: 4707c, 1966]; (b) Laky, J.; Szabo, P.; Marko, L. Acta. Chem. Acad. Sci. Hung. 1965, 46, 247; [Chem. Abstr. 64: 6511e, 1966]; (c) Reference 323, p 58.

^{415.} Ohkuma, T.; Koizumi, M.; Yoshida, M.; Noyori, R. Org. Lett. 2000, 2, 1749.

^{416.} Reference 323, p 69.
the cleavage of one ester linkage in the diolide dicrotaline (397) to give 398.417



4.8.E. Hydrogenation of Other Heteroatom Functional Groups

Catalytic hydrogenation can be applied to many functional groups, including halides, but there are problems, including poor reactivity, overreduction or competing side reactions, particularly with nitriles and halides. Nitriles are commonly hydrogenated to the amine in good yield via an imine intermediate, and nucleophilic addition of unreacted amine can lead to dimers or polyalkylated species as the final product. Reduction of propanenitrile with a rhodium catalyst gave dipropylamine, for example, after hydrogenolysis of the initially formed condensation product.⁴¹⁸ Reduction of propanenitrile with platinum or palladium catalysts gave the trisubstituted amine (tripropylamine), but rhodium oxide (Rh₂O₃) gave primarily the monoamine. Nickel, nickel boride (NiB) and cobalt are the best catalysts for conversion of low molecular weight nitriles to primary alkyl amines.^{419,420} Isolation of the amine product is sometimes difficult, and it is often isolated as its hydrochloride salt. Clive⁴²¹ found that hydrogenation of **399**, in the presence of several equivalents of chloroform, which served as a controlled source of HCl,⁴²² gave amine **400** in high yield as part of a synthesis of brevioxime.⁴²¹



Aromatic nitriles can give mixtures of the primary amine and dibenzylamines (via the condensation reaction), but this depends on the catalyst.⁴¹⁸ Rhodium hydroxide [Rh(OH)₃] is very effective for the production of aminomethyl derivatives with repression of the condensation reaction. Hydrogenation of **401** with platinum reduced the nitro group, but not the nitrile to give **402**. Subsequent reduction with palladium gave the aminomethyl group in **403** (and also

^{417.} Devlin, J.A.; Robins, D.J. J. Chem. Soc. Chem. Commun. 1981, 1272.

^{418.} Reference 323, pp 140-141.

^{419.} Zhou, B.; Edmondson, S.; Padron, J.; Danishefsky, S.. Tetrahedron Lett. 2000, 41, 2039.

^{420.} Dutasta, J.-P.; Gellon, G.; Leuchter, C.; Pierre, J.-L. J. Org. Chem. 1988, 53, 1817.

^{421.} Clive, D.L.J.; Hisaindee, S. J. Org. Chem. 2000, 65, 4923.

^{422.} Secrist III, J.A.; Logue, M.W. J. Org. Chem. 1972, 37, 335.

reduced the chloro moiety) in Folkers and Harris' synthesis of pyridoxine.⁴²³



Hydrogenation of nitro compounds is straightforward with palladium, platinum or nickel catalysts. Palladium is the most common catalyst for both aromatic and aliphatic nitro compounds. The reduction of aromatic nitriles with hydride reagents (sec. 4.2.C.iii) gives poor results, and catalytic hydrogenation the preferred method. A synthetic example is taken from Rege and Johnson's synthesis of physostigmine.⁴²⁴ Hydrogenation of the nitro group in **404**

with a palladium-on-carbon catalyst gave a quantitative yield of aniline **405**, under relatively mild conditions. Hydrogenation using platinum oxide converts aromatic nitro compounds to aniline derivatives,⁴²⁵ even in the presence of other reducible groups.⁴²⁶



Catalytic hydrogenation is commonly used for reduction of azides, which are important substrates in [3+2]-cycloaddition reactions (sec. 11.11.H) and in rhodium-catalyzed carbene chemistry (sec. 13.9.B.ii). Azides are important precursors to amines because the N_3 moiety can be incorporated into a molecule via an S_N2 reaction in aliphatic substrates, or by aromatic substitution with aromatic substrates. A second step (reduction) is required to give the amine. An example is the palladium-catalyzed reduction of **406** to give a quantitative yield of **407**,



in Hecht and co-workers synthesis of deamidobleomycin A₂, the major catabolite of the antitumor agent bleomycin.⁴²⁷ Platinum, palladium, and nickel have been used as catalysts for this reduction, but hydrazine is sometimes added to limit the extent of hydrogenolysis. Hydrogenation

to the amine can be carried out with retention of the original configuration of the azido group.

 ^{423. (}a) Harris, S.A.; Folkers, K. J. Am. Chem. Soc. 1939, 61, 1245, 3307; (b) Harris, E.E.; Firestone, R.A.; Pfister III, K.;Boettcher, R.R.; Cross, F.J.; Currie, R.B.; Monaco, M.; Peterson, E.R.; Reuter, W. J. Org. Chem. 1962, 27, 2705.

^{424.} Rege, P.D.; Johnson, F. J. Org. Chem. 2003, 68, 6133.

^{425. (}a)Bakke, J.; Heikman, H.; Hellgren, E.B. Acta Chem. Scand. 1974, 28B, 393; (b)Bakke, J. Ibid. 1974, 28B, 134.

^{426.} Wender, P.A.; Koehler, K.F.; Wilhelm, R.S.; Williams, P.D.; Keenan, R.M.; Lee, H.Y. New Synthetic Methodology and Functionally Interesting Compounds, Yoshida, Z. (Ed.), Kodansha/Elsevier, Tokyo/ Amsterdam, 1986, pp 163-182 (Cf. p 173).

^{427.} Zou, Y.; Fahmi, N.E.; Vialas, C.; Miller, G.M.; Hecht, S.M. J. Am. Chem. Soc. 2002, 124, 9476.

Epoxides react with hydrogen and a catalyst by a hydrogenolysis reaction, but it is relatively slow and many functional groups can be reduced preferentially, which means that epoxides can be reduced if there is little or no other functionality. The use of rhodium on carbon (Rh/C)⁴²⁸ or Wilkinson's catalyst⁴²⁹ usually avoids reduction of the epoxide. Predicting the direction of ring opening (regioselectivity in the reduction) in epoxides can be difficult. Symmetrical epoxides typically show delivery of hydrogen to both carbons of the oxirane ring, and Rylander discussed the various factors that influence this delivery.⁴³⁰ Prediction is usually difficult, but it has been observed that addition of hydroxide to the reaction medium influences the regioselectivity of the reduction. Hydrogenation of 1-octyloxirane (**408**) with Raney nickel gave 1-decanol, but hydrogenation using Raney nickel mixed with NaOH gave 2-decanol (**409**).⁴³¹

$$\begin{array}{c} \text{Me} \overbrace{C_7H_{15}}^{\text{Me}} \overbrace{NaOH}^{\text{Me}} \overbrace{O}^{\text{C}_7H_{15}} \xrightarrow{H_2} \text{HO} \overbrace{C_7H_{15}}^{\text{H}_2} \xrightarrow{H_2} \text{HO} \overbrace{C_7H_{15}}^{\text{C}_7H_{15}} \xrightarrow{H_2} \xrightarrow{H_2} \text{HO} \overbrace{C_7H_{15}}^{\text{C}_7H_{15}} \xrightarrow{H_2} \xrightarrow{H_2} \text{HO} \overbrace{C_7H_{15}}^{\text{C}_7H_{15}} \xrightarrow{H_2} \xrightarrow{H_$$

Hydrogenation of α , β -epoxyketones generally gives the β -hydroxy ketone,⁴³² as in the conversion of **410** to **411**.⁴³³ If other substituents (electron releasing or withdrawing) are attached to the β -position, the direction of reduction is less predictable. Reduction of aziridines



by hydrogenolysis is similar to that of epoxides and usually occurs at the less hindered C-N bond.^{434,435}

4.8.F. Hydrogenolysis Reactions

Halides are commonly incorporated into organic molecules, but in many cases they must be removed. One method is reduction to the corresponding hydrocarbon by hydrogenolysis. Raney nickel can be used, as in reduction of the iodomethyl furanose derivative **412** to the methoxy lactol **413**.⁴³⁶ Problems arise with many catalysts when the substrate contains alkenyl and

- 430. Reference 324, pp 260-265.
- 431. (a) Newman, M.S.; Underwood, G.; Renoll, M. J. Am. Chem. Soc. 1949, 71, 3362; (b) Reference 324, p 261; (c) also see Mitsui, S.; Imaizumi, S.; Hisashige, M.; Sugi, Y. Tetrahedron 1973, 29, 4093 and Sokol'skaya, A.M.; Reshetinikov, S.M.; Bakhanova, E.N.; Kuzembaev, K.K.; Anchevskaya, M.N. Khim. Khim. Tekhnol. (Alma-ata) 1966, 5, 3 [Chem. Abstr. 69: 67027g 1968].
- 432. McCurry, Jr., P.M.; Singh, R.K. J. Org. Chem. 1974, 39, 2316.
- 433. Strike, D.P.; Smith, H. Tetrahedron Lett. 1970, 4393.
- 434. Reference 324, p 267.
- 435. Sugi, Y.; Mitsui, S. Bull. Chem. Soc. Jpn. 1969, 42, 2984.
- 436. Schuler, H.R.; Slessor, K.N. Can. J. Chem. 1977, 55, 3280.

^{428.} Tarbell, D.S.; Carman, R.M.; Chapman, D.D.; Cremer, S.E.; Cross, A.D.; Huggman, K.R.; Kunstmann, M.; McCorkindale, N.J.; McNally, Jr., J.G.; Rosowsky, A.; Varino, F.H.L.; West, R.L. J. Am. Chem. Soc. 1961, 83, 3096.

^{429.} Sharpless, K.B.; Behrens, C.H.; Katsuki, T.; Lee, A.W.M.; Martin, V.S.; Takatani, M.; Viti, S.M.; Walker, F.J.; Woodard, S.S. Pure Appl. Chem. 1983, 55, 589.

carbonyl functional groups. Hydrogenation with palladium catalysts, for example, commonly removes halogen along with the functional group. If the halogen is to remain in the molecule, platinum is the preferred catalyst.

$$I \xrightarrow{0} OMe \xrightarrow{H_2, Ni(R), KOH} Me \xrightarrow{Me} OMe \xrightarrow{Me} OMe \xrightarrow{0} OMe$$

The hydrogenolysis reaction is an important part of many syntheses that involve protection of functional groups (secs. 7.3.A, 7.3.C). Protection of alcohols and amines with a benzyl group is common (secs. 7.3.A, 7.3.C.i).⁴³⁷ Palladium favors hydrogenolysis, and it is commonly used for PhCH₂-//-O or PhCH₂-//-N cleavage, leading to toluene and the alcohol or amine. An example of C-N cleavage is the conversion of benzylamine **414** to amine **415** (>90% yield) in a synthesis of 2-epi-perhydrohistrionicotoxin by Hsung and co-workers.⁴³⁸ Hydrogenolysis is the common method for removal of the benzyloxycarbonyl (Cbz; benzyl carbamate) group, a carbamoyl protecting group often used to protect amines (sec. 7.3.C.iii). This reaction is illustrated by conversion of the PhCH₂O₂CNH- group in **416** to the amine unit in **417** (80% yield), as part of de Meijere and Larionov's synthesis of belactosin C (**417**)⁴³⁹ Note that hydrogenolysis of the benzyl ester (-CO₂Bn) occurred under these conditions to give the corresponding carboxylic acid moiety. In multi-functional molecules, reduction of other functional groups can compete with hydrogenolysis of the O-Bn bond.⁴⁴⁰



Dithianes and dithiolanes are generated from the reaction of dithiols with aldehydes and ketones, and they are commonly used to generate sulfur stabilized carbanions (sec. 8.6), or as

^{437. (}a) Wuts, P.G.M.; Greene, T.W. Protective Groups in Organic Synthesis 3rd ed, Wiley, New York, 1999; (b) Wuts, P.G.M.; Greene, T.W. Protective Groups in Organic Synthesis 2nd ed, Wiley, New York, 1991; (c) Greene, T.W. Protective Groups in Organic Synthesis Wiley, New York 1981; (d) Wuts, P.G.M.; Greene, T.W. Protective Groups in Organic Synthesis 4th ed., Wiley, New Jersey, 2006.

^{438.} McLaughlin, M.J.; Hsung, R.P.; Cole, K.P.; Hahn, J.M.; Wang, J. Org. Lett. 2002, 4, 2017.

^{439.} Larionov, O.V.; de Meijere, A. Org. Lett. 2004, 6, 2153.

^{440.} For an example, see Burgstahler, A.W.; Weigel, L.O.; Sanders, M.E.; Shaefer, C.G.; Bell, W.J.; Vuturo, S.B. J. Org. Chem. 1977, 42, 566.

carbonyl protecting groups (sec. 7.3.B.ii). In addition, sulfur compounds such as sulfoxides and sulfones are important for C-C bond forming reactions via the sulfur carbanions (sec. 8.6.A). In many cases, the sulfur group must be removed from the molecule after its synthetic use has been accomplished. Bivalent sulfur is a common poison of heterogeneous catalysts, and the affinity of sulfur for nickel makes Raney nickel an effective reagent for hydrogenolysis of the C-S bond. Reduction of the dithiolane is usually accomplished by simply heating with Raney nickel in ethanol or methanol, without adding hydrogen gas.⁴⁴¹ An example is the desulfurization of **418** to give **419** in 62% yield, in a synthesis of naphthalene analogs of lignans by Medarde and co-workers.⁴⁴²



4.8.G. Hydrogenation of Aromatic and Heteroaromatic Hydrocarbons

Aromatic hydrocarbons and heterocycles are important in many natural products and reduction of the aromatic ring is very important from a synthetic viewpoint. Clearly, the simplest example is reduction of benzene to cyclohexane, and it requires vigorous reaction conditions unless rhodium catalysts are used. Rylander showed the order of various catalysts for the hydrogenation of benzene to be

Rh > Ru >> Pt > Pd >> Ni > Co

Rhodium and ruthenium are used to avoid hydrogenolysis. The catalyst of choice changes somewhat with fused ring aromatic hydrocarbons. The relative order for reduction of naphthalene to tetralin (**420**) is⁴⁴³

Pd > Pt > Rh > Ir > Ru

This order is due, in part, to the slow reduction of the aromatic ring in 420 with palladium. Rhodium gives initial reduction of naphthalene to 420, but further reduction to decalin (421) is so rapid that 420 is a minor constituent of the final product mixture.

^{441.} For an example, see Davis, F.A.; Chao, B.; Fang, T.; Szewczyk, J.M. Org. Lett. 2000, 2, 1041.

^{442.} Madrigal, B.; Puebla, P.; Peláez, R.; Caballero, E.; Medarde, M. J. Org. Chem. 2003, 68, 854.

^{443.} Reference 323, p 180.



When the aromatic ring is substituted, catalytic hydrogenation can be complicated by side reactions. Reduction of phenols initially gives enol products, but these are usually converted to cyclohexenone or cyclohexanedione derivatives. An example is the reduction of 422 to 423,⁴⁴⁴ which stands in contrast to the reduction of 424, which in the presence of excess hydrogen gave cyclohexane derivative **425**.⁴⁴⁵ Note the selectivity of the reduction for the all cis geometry in 425. Palladium or platinum catalysts lead to significantly less stereoselectivity in this type of reduction. Catalytic hydrogenation is usually very selective for electron-rich aromatic rings if there is another aromatic ring that bears electron-withdrawing substituents. A simple benzene ring is reduced faster than a ring with an electron-withdrawing group attached to it. Reduction of 1-naphthalenecarboxylic acid (426) with Ni(R) led to selective reduction of the more electron-rich ring to give **427**.⁴⁴⁶ An example of hydrogenation of a benzene ring in a synthetic sequence is the conversion of 428 to 429 in 74% yield, as part of Denmark and Fu's synthesis of the serotonin antagonist LY426965.⁴⁴⁷ Note the selective hydrogenation of only one phenyl group. The first hydrogenation gave a mixture of 429 and the tetrahydro derivative (the cyclohexene compound). Hydrogenation of this mixture in the second step gave 429 in 74% overall yield. Prolonged hydrogenation of **428** gave reduction of both phenyl groups.⁴⁴³



Catalytic hydrogenation of aniline derivatives is often accompanied by disubstituted amine products, as in the formation of dicyclohexylamine (432) from aniline.⁴⁴⁸ The reactive intermediate in the reduction is an initially formed imine 430, which is in equilibrium with the enamine under the reaction conditions. Reduction of 430 gives cyclohexylamine, which reacts with 430 to give 431. Under the reaction conditions, 431 loses cyclohexylamine to give an imine (or an iminium salt). This intermediate then reacts with additional hydrogen to give the

^{444. (}a) Mokotoff, M.; Cavestri, R.C. J. Org. Chem. 1974, 39, 409; (b) Reference 323, pp 194-195.

^{445.} Gensler, W.J.; Solomon, P.H. J. Org. Chem. 1973, 38, 1726.

^{446.} Bohlmann, F.; Eickeler, E. Chem. Ber. 1979, 112, 2811.

^{447.} Denmark, S.E.; Fu, J. Org. Lett. 2002, 4, 1951.

^{448.} Reference 323, p 187.

isolated product, 432. This process is analogous to the dimerization reactions observed in the



LiAlH₄ reduction of aliphatic nitriles (sec. 4.2.C.iii for the formation of dipropylamine from propanenitrile). This side reaction can usually be limited to a small percentage by the use of ruthenium or rhodium catalysts, allowing isolation of the amine. Note that enamines can be directly reduced to the amine by catalytic hydrogenation.⁴⁴⁹ The order of least coupling (with Ru) to most coupling (with Pt) is⁴⁴⁸

$$Ru < Rh \ll Pd < Pt$$

The product(s) formed by reduction of heterocyclic aromatic compounds varies with the number of rings, the heteroatom and its position in the molecule, as well as the catalyst. For pyridine and pyrrole derivatives, rhodium is the most common catalyst, and acidic media are used to form the corresponding salt, which is more easily reduced. Hydrogenation of pyrrole is more difficult, which is illustrated by the observation that hydrogenation of 2-vinyl pyrrole (**433**) with 3 atmospheres of hydrogen gave 2-ethyl pyrrole (**434**) in 81% yield without reduction of the pyrrole ring.⁴⁵⁰ Hydrogenation of the pyrrole ring is possible under acidic conditions, illustrated by hydrogenation of the previous reaction product (**434**) to give **435**.⁴⁵⁰ Rhodium catalysts are usually preferred in low-pressure hydrogenations to reduce heterocyclic aromatic rings.



Both platinum and palladium catalysts can be used for the hydrogenation of heteroaryl derivatives, although platinum is more common. Selective reduction of the heterocyclic ring in 8-methyl-7-hydroxy isoquinoline (**436**) gave **437** in 67% yield, in Woodward and von E. Doering's synthesis of quinine.⁴⁵¹

^{449.} Wu, P.-L.; Chu, M.; Fowler, F.W. J. Org. Chem. 1981, 53, 963.

^{450.} Cantor, P.A.; Vanderwerf, C.A. J. Am. Chem. Soc. 1958, 80, 970.

^{451. (}a) Woodward, R.B.; Doering, W.E. J. Am. Chem. Soc. 1944, 66, 849; (b) Idem Ibid. 1945, 67, 860.



Reductive alkylation of heteroaromatic rings is possible using catalytic hydrogenation.⁴⁵² Reduction of heteroaryl ammonium salts is also possible. In an example taken from a synthesis of the trail pheromone of the Pharaoh ant (**440**) by Sonnet and Oliver, treatment of **438** with triphenylphosphine•bromine led to pyridinium salt **439**. Subsequent hydrogenation over PtO₂ gave 3-butyl-5-methyloctahydroindolizine **440**.⁴⁵³



Oxygenated heterocycles are reduced with hydrogen but are prone to hydrogenolysis, especially when platinum is used. Hydrogenation of furan derivatives uses palladium, rhodium, or ruthenium catalysts to minimize this problem. When the reaction is done at higher temperatures and under acidic conditions, however, ring cleavage can occur via hydrogenolysis. Hydrogenation of furan to THF is straightforward when a mixed catalyst of 70% rhodium + 30% platinum is used.⁴⁵⁴ The reduction of disubstituted furan **441** to **442**, in the Gerlach et al. synthesis of 8-*epi*-nonactic acid used a rhodium catalyst.⁴⁵⁵ Reduction of thiophene derivatives can be difficult because bivalent sulfur is a common poison for heterogeneous catalysts. This problem can be circumvented or diminished by using a large excess of a heterogeneous catalyst (high catalyst loading). As an example, thiophene was reduced to perhydrothiophene in 71% yield, but only when the molar ratio of palladium to thiophene was 2:1 or greater.⁴⁵⁶



4.8.H. Asymmetric Catalytic Hydrogenation

Unsymmetrical ketones or substituted alkenes have prochiral carbons, and hydrogenation gives

456. Mozingo, R.; Harris, S.A.; Wolf, D.E.; Hoffhine, Jr., C.E.H.; Easton, N.R.; Folkers, K. J. Am. Chem. Soc. 1945, 67, 2092.

^{452.} Szychowski, J.; MacLean, D.B. Can. J. Chem. 1979, 57, 1631.

^{453.} Oliver, J.E.; Sonnet, P.E. J. Org. Chem. 1974, 39, 2662.

^{454.} Reference 323, p 228

^{455. (}a) Gerlach, H.; Wetter, H. Helv. Chim. Acta 1974, 57, 2306; (b) Gerlach, H.; Oertle, K.; Thalmann, A.; Servi, S. Ibid. 1975, 58, 2036.

a product that contains one or more stereogenic centers. Therefore, stereoselectivity in the hydrogenation process is an important issue. Asymmetric induction during hydrogenation is possible if a chiral catalyst is used. With heterogeneous catalysts, asymmetric induction usually involves addition of a metal catalyst to a chiral coordinating molecule or a chiral medium⁴⁵⁷ such as silk fibroin,⁴⁵⁸ (a natural structural protein from silk), which gave products with up to 70% ee (see sec. 1.4.F for a definition of % ee). Other chiral additives include palladium on poly-(*L*)-leucine,⁴⁵⁹ Pd/C with (*S*)-methionine,⁴⁶⁰ palladium on silica gel in the presence of a chiral alkaloid such as narcotine,⁴⁶¹ and platinum with *l*-menthoxy acetate or tartaric acid.⁴⁶² Hydrogenation of a chiral substrate with a heterogeneous catalyst can show enantioselectivity, but problems associated with chemisorption sometimes lead to racemization or bond migration. These secondary reactions are less of a problem with homogeneous catalysts. Indeed, soluble, chiral homogeneous catalysts are usually the best choice in catalytic hydrogenation, especially for alkenes. The occasionally poor activity of homogeneous catalysts with heterocyclic functional groups can limit their utility.

A common way to generate a chiral catalyst involves a modification of Wilkinson's catalyst (**336**) in which an optically active tertiary phosphine, bis- or tris(phosphines) are used as ligands in place of triphenyl-phosphine. If the phosphorous atom of the added phosphine is the stereogenic center, the optical yields are usually 4-22%, as in the conversion of atropic acid (**443**) to hydratropic acid (**444**) with 22% ee.⁴⁶³ An example of this type of phosphine is (–)-methylpropylphenylphosphine. Chiral bis(phosphines) are commonly used, including **445** (called dipamp)⁴⁶⁴ and **446** (called R-camp).⁴⁶⁵



As noted in Section 1.4.A, phosphines are configurationally stable if the temperature is *below* \sim 130°C, which is in sharp contrast to amines which show fluxional inversion even at low temperatures. The configurational stability of chiral phosphines allows their preparation,

- 462. Nakamura, Y. J. Chem. Soc. Jpn. 1940, 61, 1051 [Chem. Abstr. 37: 3772, 1943].
- 463. (a) Knowles, W.S.; Sabacky, M.J. J. Chem. Soc. Chem. Commun. 1968, 1445; (b) Cullen, W.R.; Fenster, A.; James, B.R. Inorg. Nucl. Chem. Lett. 1974, 10, 167.
- 464. (a) Brown, J.M.; Chaloner, P.A. J. Chem. Soc. Chem. Commun. 1980, 344; (b) Idem Ibid. 1978, 321; (c) Idem Tetrahedron Lett. 1978, 1877; (d) Idem J. Am. Chem. Soc. 1980, 102, 3040.
- 465. Knowles, W.S.; Sabacky, M.J.; Vineyard, B.D. Adv. Chem. Ser, 1974, 132, 274.

^{457. (}a) Reference 333, pp 74-80; (b) Reference 231, pp 292-302 and citations cited therein.

 ⁽a) Reference 323, pp 292, 297; (b) Reference 333, p 74; (c) Akabou, S.; Sakurai, S.; Izumi, Y.; Fujii, Y. Nature (London) 1956, 178, 323.

^{459.} Beamer, R.L.; Fickling, C.S.; Ewing, J.H. J. Pharm. Sci. 1967, 56, 1029.

^{460.} Senoh, S.; Ouchi, S.; Tsunoda, K. Jpn. Patent 13, 307, 1963 [Chem. Abstr. 60: 3092h 1964].

^{461.} Padgett, R.E.; Beamer, R.L. J. Pharm. Sci. 1964, 53, 689.

isolation and even optical resolution, but they are not always easy to synthesize. A useful alternative is to attach an achiral phosphine to a stereogenic center at carbon, and most are derivatives of 1,2-diphenylphosphinoethane (called diphos or dppe, **447**). When these phosphine ligands are used to form homogeneous catalysts, the enantioselectivity can be very good, if the alkene substrate is properly chosen. Some of the more popular chiral phosphine ligands include **448** (called diop),⁴⁶⁶ **449** (called chiraphos),⁴⁶⁷ **450** (called prophos),⁴⁶⁸ the ferrocenyl derivative **451**,⁴⁶⁹ and **452** (called bppm).⁴⁷⁰ These bis(phosphine) ligands are often coordinated to rhodium⁴⁷¹ in modified Wilkinson's catalysts.



One of the more important applications of chiral hydrogenation catalysts is the preparation of chiral α -amino acids. Koenig correlated the % ee for the reduction of **453** to **454** with rhodium catalysts prepared from several chiral phosphine ligands (see Table 4.14).⁴⁷¹ In general, reduction of **453** gave the enantiomer of **454** with the absolute configuration opposite that of the chiral phosphine [i.e., $(RR) \rightarrow (S)$; $(SS) \rightarrow (R)$; $(R) \rightarrow (S)$; $(S) \rightarrow (R)$]. One complicating factor is that some isomerization $(E) \rightarrow (Z)$ occurs in **453** during hydrogenation, depending on the solvent and the catalyst. Reduction of **453** in THF with **447** showed 23% isomerization. Reduction with (RR)-diop (**448**) gave 20% isomerization, but dipamp (**445**) showed 0% isomerization. Isomerization was more extensive in ethanol (28% with diphos, 35% with diop, and 6% with dipamp). When benzene was used, no isomerization was observed with any of these catalysts.^{472b}

^{466. (}a) Dang, T.P.; Kagan, H.B. J. Chem. Soc. Chem. Commun. 1971, 481; (b) Kagan, H.B.; Dang, T.P. J. Am. Chem. Soc. 1972, 94, 6429; (c) Levi, A.; Modena, G.; Scorrano, G. J. Chem. Soc. Chem. Commun. 1975, 6.

^{467. (}a) Chan. A.S.C.; Halpern, J. J. Am. Chem. Soc. 1980, 102, 838; (b) Chua, P.S.; Roberts, N.K.; Bosnich, B.; Okrasinski, S.J.; Halpern, J. J. Chem. Soc. Chem. Commun. 1981, 1278.

^{468. (}a) Fryzuk, M.D.; Bosnich, B. J. Am. Chem. Soc. 1978, 100, 5491; (b) Idem Ibid. 1977, 99, 6262.

^{469.} Hayashi, T.; Yamamoto, K.; Kumada, M. Tetrahedron Lett. 1974, 4405.

^{470.} Achiwa, K. J. Am. Chem. Soc. 1976, 98, 8265.

^{471.} Koenig, K.E. in *Catalysis of Organic Reactions*, Kosak, J.R. (Ed.), Marcel Dekker, New York, *1984*, pp 63-77, cf. pp 72-73.

 ^{472. (}a) Vineyard, B.D.; Knowles, W.S.; Sabacky, M.J.; Bachmann, G.K.; Weinkauff, D.J. J. Am. Chem. Soc. 1977, 99, 5946; (b) Koenig, K.E.; Knowles, W.S. Ibid. 1978, 100, 7561.

Ph CO ₂ H NHAc	H_2, RhL_4^*	Ph CO ₂ H NHAc 454
Ligand	<u>% ee</u>	(<u>R) or (S)</u>
(RR)-448	85	(S)
(SS)-449	95+	(<i>R</i>)
(RR)-450	90	(S)
451	93	

<u>94</u>

15

(*RR*)-445

(R)-446

(S)

(S)

Table 4.14. Effect of Chiral Phosphine Ligands on the Asymmetric Hydrogenation of 453

When these ligands react with rhodium salts, many intermediate metal complexes can be formed, including Rh(diphos)cod⁺, Rh(diphos)Ac, Rh(dipamp)₂, Rh(diop)NBD⁺, and Rh(camp)₂ COD⁺. In work by Halpern and co-workers, several intermediates in the hydrogenation of **453** with rhodium catalysts were characterized.^{467a} An initial square planar Rh(I) coordination complex (**455**) was detected by NMR (¹H, ¹³C, ³¹P), and its tetrafluoroborate salt was isolated and identified by X-ray crystallography.⁴⁷³ Lowering the temperature, and using the same NMR techniques allowed observation of a square-planar Rh(III) intermediate (**456**), generated after transfer of hydrogen to the π bond.^{467a,473} Halpern presented a mechanistic rationale for the reduction of **457** with this catalyst, based on these intermediates.⁴⁷⁴ Halpern and co-workers suggested transformation of a square planar complex to an octahedral complex as the hydrogens are transferred from rhodium to carbon, in a stepwise manner.^{467,473} Chiral ligands generate facial selectivity in the complex during the hydrogen transfer.



[Reprinted with permission from Chan. A.S.C.; Halpern, J. J. Am. Chem. Soc. 1980, 102, 838. Copyright © 1980 American Chemical Society.]

4.9. DISSOLVING METAL REDUCTIONS

Reduction involves the gain of electrons by an organic species, as described in this chapter. Many metals and metal salts can transfer electrons to an organic substrate, reducing them with concomitant oxidation of the metal. This section will describe the more common metals used

^{473.} Chan, A.S.C.; Pluth, J.J.; Halpern, J. Inorg. Chim. Acta 1979, 37, 2477.

^{474.} Halpern, J. in Reference 325d, pp 3-22.

for this purpose as well as the functional groups that are reduced by them. Electron transfer in an electrolytic cell accomplishes essentially the same reactions as treatment with alkali metals, but there are some interesting differences.

4.9.A. Reduction with Alkali Metals

Metals can be used to reduce organic molecules in the presence of a proton transfer agent. Alkali metals can transfer an electron to some organic molecules, but reduction requires delivery of protons from an acidic solvent (with an X–H bond) to reactive intermediates. Transfer of an electron to an organic molecule generates a metal cation along with the radical anion derived from the organic fragment. Water, alcohol or ammonia are common acidic solvents used to quench the radical anion, but primary or secondary amines can also be used. The ability of a metal to reduce organic molecules is directly related to its ability to release electrons (reduction potential), and Hudlick'y tabulated these values for several alkali and transition metals.⁴⁷⁵ Based on standard reduction potentials,⁶ lithium and potassium followed closely by sodium were the most effective electron transfer metals in this series. It is therefore not surprising that these metals are used most often for reduction of organic molecules. This type of reduction is commonly called a **dissolving metal reduction**.

Metal reduction is most commonly applied to polarized organic substrates containing multiple bonds (C=O, C=N, C=N). Isolated alkenes are not easily reduced, which is a major difference from the related electrolytic reductions to be discussed in Section 4.9.J. Alkenes that are conjugated to a phenyl ring, another double bond or an aromatic ring are reduced quite easily, however, as in the conversion of **457** to **458** in 97% yield.⁴⁷⁶ Alkynes are generally converted to the trans alkene. The alkyne unit in **459** was reduced to the trans-alkene unit in **460**, for example, in a synthesis of (–)-pironetin by Dias and co-workers.⁴⁷⁷ Aromatic rings, halides, and sulfur derivatives are also reduced. Complete reduction of the aromatic ring is possible, especially with heterocyclic rings including pyridine and furan derivatives.



Conjugated dienes are reduced, usually via 1,4-addition to give an alkene. When the conjugated diene unit in **461** was treated with sodium metal in ammonia, a 65% yield of **462** was obtained

^{475.} Reference 7, p 25.

^{476.} McEnroe, F.J.; Fenical, W. Tetrahedron 1978, 34, 1661.

^{477.} Dias, L.C.; de Oliveira, L.G.; de Sousa, M.A. Org. Lett. 2003, 5, 265.

as part of Meyers and Lemieux's synthesis of (–)-trichodiene.⁴⁷⁸ As expected, a mixture of 1,4-reduction (to give **462**) and 1,2-reduction (to give **463**) was observed (in a ratio of 85:15), which is common with this type of reduction. Note that the nonconjugated *exo*-methylene group of the five-membered ring (in **461**) was not reduced under these conditions.



Dissolving metal conditions are capable of reducing many organic functional groups, often with excellent chemo-, regio- and stereoselectivity. The choice of solvent is important, often changing the course of a reaction and having a great influence of the yield and ease of isolation of the products. Liquid ammonia is commonly used, often in conjunction with alcohols. Low molecular weight amines and ethylenediamine can be used in reductions with lithium metal.⁴⁷⁹ The most common applications for this reaction include reduction of alkynes, conjugated carbonyls and Birch-type reductions of aromatic rings.

4.9.B. Reduction of Carbonyl Compounds

Metal reduction of ketones and aldehydes begins with electron transfer from the metal to the carbonyl, forming a ketyl (a radical anion). If we use acetone as a typical example, the mechanism of reduction involves transfer of an electron from the metal to the carbonyl π bond giving a radical anion with two canonical forms (464).⁴⁸⁰ There are two competing pathways for the ketyl, reduction or radical coupling to give 467, which gives diol 468 after protonation. If we want to facilitate reduction, a protic solvent such as alcohol or water is added to transfer a proton to the oxygen in an acid-base reaction (giving 465). Protonation, followed by a second electron transfer from the metal, gives the carbanionic species 466. A second proton is transferred from the solvent to give the final reduction product, 2-propanol.



When a ketone or aldehyde is part of a substrate bearing a stereogenic center elsewhere in the

^{478.} Lemieux, R.M.; Meyers, A.I. J. Am. Chem. Soc. 1998, 120, 5453.

^{479.} Garst, M.E.; Dolby, L.J.; Esfandiari, S.; Fedoruk, N.A.; Chamberlain, N.C.; Avey, A.A. J. Org. Chem. 2000, 65, 7098.

^{480.} Reference 7, p 23.



molecule, reduction can proceed with good diastereoselectivity. Reduction of **469** from the exo- face led to a quantitative yield of **470**, in Takasu and Ihara's synthesis of culmorin.⁴⁸¹ Conjugated ketones are reduced selectivity at

the alkene moiety and there is usually a preference for the product with a trans-ring juncture (see below).⁴⁸²

Formation of diol **468**, as mentioned above, can arise by radical coupling of **464** to give **467** or by radical coupling of **465** to give diol **468** directly. The coupling reaction is called the **pinacol coupling** (see sec. 13.8.D for a more complete description),⁵⁶⁷ and is a useful method for the synthesis of 1,2-diols⁴⁸³ where aromatic ketones give the best yields. Pinacol coupling is best accomplished by using a mixture of magnesium and magnesium iodide (Mg + MgI₂), although magnesium amalgam (Mg/Hg) can also be used.^{484a} Pinacol coupling of acetone leads to a diol called pinacol (2,3-dimethyl-2,3-butanediol), which gives the reaction its name.



The electron transfer/proton transfer mechanism presented for ketone reduction is under thermodynamic control, and leads to the more stable trans-alcohol.^{379b} Conjugated ketones react to give alcohols via 1,4-reduction,^{379b} which is also explained by the ketyl mechanism. Transfer of an electron gives a very stable, resonance-delocalized ketyl (471). Protonation gives an allylic enol radical (472), and transfer of a second electron gives 473. Proton transfer generates the enol, which tautomerizes to the ketone product. An example is the dissolving metal

reduction of **474** to give **475** in quantitative yield, in Covey and co-worker's synthesis of deoxycholic acid.⁴⁸⁵ Note that triethylamine was added after quenching with ammonium



^{481.} Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. J. Org. Chem. 2000, 65, 4112.

^{482. (}a) Stork, G.; McMurry, J.E. J. Am. Chem. Soc. 1967, 89, 5464; (b) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R.V.; Tsuji, J. Ibid. 1965, 87, 275.

^{483.} Schreibman, A.A.P Tetrahedron Lett. 1970, 4271.

^{484. (}a) Adams, R.; Adams, E.W. Org. Synth. Coll. Vol. 1 1932, 459; (b) Torii, S.; Inokuchi, T.; Kawai, K. Bull. Chem. Soc. Jpn. 1979, 52, 861.

^{485.} Katona, B.W.; Rath, N.P.; Anant, S.; Stenson, W.F.; Covey, D.F. J. Org. Chem. 2007, 72, 9298.

chloride to ensure that the ketals were not removed by residual acid (see sec. 7.3.B.). Pinacol coupling is also a competing side reaction with conjugated ketones.⁴⁸⁶ Conjugated reduction of α , β -unsaturated esters has been reported using Mg in methanol.⁴⁸⁷

4.9.C. Reduction of Alkynes

An important use of metal reduction is to convert alkynes to trans-alkenes, as illustrated by the conversion of **476** to **477** in 92% yield in Koert and Emde's synthesis of squamocin A.⁴⁸⁸



In the general case, the reaction is initiated by electron transfer to the alkyne (see **478**) to give a radical anion (**479**). Electron repulsion of the radical orbital and the carbanion orbital dictates that they be as far apart as possible, which leads to the trans-geometry. Protonation of **479** from either ammonia or an added alcohol co-solvent gives a vinyl radical, **480** and a second electron transfer leads to vinyl carbanion **481**. A second protonation step gives the final trans alkene product. Reduction using either lithium or sodium in liquid ammonia gives primarily the trans alkene,^{486b} but increasing amounts of the cis alkene are observed in protonic solvents such as ethanol. Reduction of terminal alkynes is complicated by the acidity of the alkyne hydrogen, which reacts with sodium or lithium to form an acetylide anion (secs. 2.2.A, 8.3.B). Reduction to the alkene is possible, however, by controlling the stoichiometry of the reagent. Reaction of propyne with sodium initially generates the acetylide (**482**), and in the presence of additional alkyne, **482** is reduced to 1-propene as shown.⁴⁸⁹ If sodium becomes the limiting reagent, reduction to the alkene is possible. An example is the reduction of 1-octyne to 1-octene in 90% yield (ratio of alkene/sodium = 11.5/1).^{486b}



^{486. (}a) Wiemann, J.; Monot, M.R.; Dana, G.; Chuche, J. Bull. Soc. Chim. Fr. 1967, 3293; (b) Kochansky, J.P.; Cardé, R.T.; Taschenberg, E.F.; Roelofs, W.L. J. Chem. Ecol. 1977, 3, 419.

^{487.} For an example taken from a synthesis of (+)-sertraline, see Chandrasekhar, S.; Reddy, M.V. *Tetrahedron* 2000, 56, 1111.

^{488.} Emde, U.; Koert, U. Eur. J. Org. Chem. 2000, 1889.

^{489.} Henne, A.L.; Greenlee, K.W. J. Am. Chem. Soc. 1943, 65, 2020.

Low molecular weight amines such as ethylamine and methylamine are often substituted for ammonia when higher reaction temperatures are required (i.e., > -33 °C). Changing to an ether solvent also leads to interesting differences in reactivity. As House pointed out,⁴⁹⁰ reduction of diphenylacetylene (**483**) with sodium in THF (-78 °C) gave only 25% of the expected *trans*-stilbene (**487**), 30% of the completely reduced 1,2-diphenylethane and unreacted starting material. Similar reduction with lithium in THF gave a quantitative yield of the deuterated cis alkene **485** upon quenching with *d*-methanol, presumably due to the greater stability of the dimeric dilithio species (**484**) relative to the disodio species **486**.



The functional group transforms possible are:



4.9.D. Hydrogenolysis

Hydrogenolysis may be a competing reaction in dissolving metal conditions, and is particularly useful for the cleavage of *O*-benzyl and *N*-benzyl derivatives. It is widely used as a useful alternative to catalytic hydrogenation. Treatment with sodium in ammonia cleaves an *O*-benzyl group or an *N*-benzyl group. An example of the latter reaction is the conversion of **488** to **489** (in 80% yield), in Passarella and co-worker's synthesis of aloperine.⁴⁹¹ Note that the byproduct is toluene and that ethylenediamine is the solvent. It is also possible to cleave other reactive C–O (or C–N) bonds. Allylic and benzylic acetates, for example, are cleaved to the hydrocarbon, as shown in a synthesis of ottelione A by Katoh and co-worker's,⁴⁹² in which the reaction of **490** with lithium and ammonia in THF gave a 98% yield of **491**. Note that both OAc units in **490** are reduced to the alcohol as well.



^{490.} Reference 16, p 207 and references cited therein.

- 491. Passarella, D.; Angoli, M.; Giardini, A.; Lesma, G.; Silvani, A.; Danieli, B. Org. Lett. 2002, 4, 2925.
- 492. Araki, H.; Inoue, M.; Katoh, T. Org. Lett. 2003, 5, 3903.



The hydrogenolysis reaction with metals in ammonia involves transfer of an electron to the heteroatom, with cleavage of the C-X bond. Electron transfer to benzyl ether (**492**), for example, generates a radical anion such as **493**. Homolytic cleavage liberates an alkoxide and the benzyl radical (**494**). This benzyl radical removes a hydrogen atom from a hydrogen donor in the medium (solvent, starting ether, etc.) to give toluene as the other reduction product. Cleavage to an alkoxy radical and a benzyl carbanion is also possible, although formation of the resonance stabilized benzyl radical is a more reasonable mechanistic rationale.



Since the mechanism involves electron transfer to a heteroatom rather than carbon, vinyl or aryl derivatives are easily reduced under these conditions. Many functional groups can be reduced, depending on their ability to accept an electron. Cyclopropane rings are opened under these conditions to give methyl derivatives.⁴⁹³ The bridging cyclopropane moiety in **495**, for example, was opened with lithium and ammonia to give **496** in 85% yield as part

of Srikrishna and Vijaykumar's synthesis of (+)-pinguisenol from (*R*)-carvone.⁴⁹⁴ Halides undergo hydrogenolysis with alkali metals, and both alkyl⁴⁹⁵ and vinyl halides give good yields of the corresponding alkene.



Hydrogenolysis of the C–S bond is rapid, and sulfides, sulfones or sulfoxides are reduced to the hydrocarbon moiety by this method.⁴⁹⁶ Since sulfur usually poisons hydrogenation catalysts, reduction with metal is a preferred method for chemoselective cleavage of the C–S bond. In a synthesis of (–)-lasubine II by Back and Hamilton,⁴⁹⁷ the sulfone group in **497** (-CHSO₂Tol) was cleaved to the hydrocarbon (-CH₂- in **498**) with lithium in liquid ammonia. Sulfides are similarly reduced.⁴⁹⁸ Sodium amalgam is another important reagent for reductive cleavage

^{493. (}a) Packer, R.A.; Whitehurst, J.S. J. Chem. Soc. Perkin Trans. 1 1978, 110; (b) Idem J. Chem. Soc. Chem. Commun. 1975, 757.

^{494.} Srikrishna, A.; Vijaykumar, D. J. Chem. Soc. Perkin Trans. 1 2000, 2583.

^{495.} Eaton, P.E.; Or, Y.S.; Branca, J.S. J. Am. Chem. Soc. 1981, 103, 2134.

^{496.} For a review that includes reductive desulfonylation, see Nájera, C.; Yus, M. Tetrahedron 1999, 55, 10547.

^{497.} Back, T.G.; Hamilton, M.D. Org. Lett, 2002, 4, 1779.

^{498.} Kodama, M.; Matsuki, Y., Itô, S. Tetrahedron Lett. 1975, 3065.

of C–S bond. In a synthesis of gymnocin A,⁴⁹⁹ Sasaki and co-workers treated sulfone **499** with Na(Hg), and obtained **500** in 75% yield. Both sulfoxides and sulfones are important in alkylation and condensation reactions of their respective sulfur-stabilized carbanions (sec. 8.6).



Epoxides are opened by dissolving metal reductions to give an alcohol, usually with good stereoselectivity and regioselectively favoring the product with oxygen at the less hindered carbon. The radical anion intermediate usually leads to the more stable trans alcohol. The presence of substituents at the epoxide-carbon can have a profound influence on the regioselectivity. In a synthesis of formal synthesis of reserpine by Shea and co-workers, reduction of **501** with sodium in ammonia gave a 50% yield of **503**.⁵⁰⁰ The regiochemical preference for **503** is driven by formation of the resonance stabilized enolate anion intermediate, **502**. Epoxides are also subject to pinacol type coupling reactions, but the yields are usually low and reduction is the major process.⁵⁰¹ Esters and lactones are usually reduced to the alcohol or diol. Anomalous reactions can occur, however, as in the reduction of a lactone to a lactol,⁵⁰² but this is common only with carbohydrates and hindered lactones.



502. Wong, C.-H.; Whitesides, G.M. J. Am. Chem. Soc. 1983, 105, 5012.

^{499.} Sasaki, M.; Tsukano, C.; Tachibana, K. Org. Lett. 2002, 4, 1747.

^{500.} Sparks, S.M.; Gutierrez, A.J.; Shea, K.J. J. Org. Chem. 2003, 68, 5274.

^{501.} Movsumzade, M.M.; Agaev, F. Kh.; Shabanov, A.L. Azerb. Khim. Zh. 1966, 38, 38 [Chem. Abstr. 67: 63653u 1967].

4.9.E. Birch Reduction

Partial reduction of aromatic rings with alkali metals⁵⁰³ is an important synthetic method because it allows one to use aromatic substitution reactions to set functionality, and reduction to a nonaromatic system then allows transforms to other compounds. When a dissolving metal reduction is carried out on an aromatic ring containing electron releasing groups (alkyl, alkoxy,

etc.) the cyclohexadiene product formed will have those groups on a vinylic carbon $(sp^2 \text{ carbon})$,⁵⁰⁴ as in the reduction of **504** to **505** in >90% yield as part of Baldwin and co-worker's synthesis of biatractylolide.⁵⁰⁵





Conversely, reduction of an aromatic ring that has an electron-withdrawing group on the ring will generate a product with that group on the sp³ carbon. Reduction of **506** led to **507**, for example.⁵⁰⁶ The electron transfer

mechanism invoked for reduction of alkynes and carbonyls also explains these results. Transfer of an electron to anisole is slower due to the OMe and leads to **508** or **509**. The proximity of the negative charge to the electron-rich oxygen in **508** destabilizes it, which leads to a preference for **509**. Protonation and a second electron transfer will lead to vinyl ether **510**. When the substituent on the aromatic ring is changed to an electron-withdrawing group (such as carboxyl), the selectivity changes. Electron transfer to benzoic acid leads to **511** or **512**. The electron-withdrawing carbonyl group stabilizes the developing negative charge in **511**, and it is preferred to **512**. The usual sequence leads to **513** as the final product. This partial reduction of aromatic rings is known as the **Birch reduction**.⁵⁰⁷ Complete reduction of the aromatic ring is also possible, especially with those molecules that contain heterocyclic rings such as pyridine or furan derivatives. A recent variation uses lithium and di-*tert*-butylbiphenyl for an ammonia-free Birch reduction.⁵⁰⁸

^{503.} For a brief review of the Birch reduction and its application to the synthesis of natural products, see Schultz, A.G. Chem. Commun. 1999, 1263.

^{504.} Zimmerman, H.E.; Wang, P.A. J. Am. Chem. Soc. 1993, 115, 2205.

^{505.} Bagal, S.K.; Adlington, R.M.; Baldwin, J.E.; Maquez, R.; Cowley, A. Org. Lett. 2003, 5, 3049.

^{506. (}a) Caluwe, P.; Pepper, T. J. Org. Chem. 1988, 53, 1786; (b) Rubin, M.B.; Welner, S. Ibid. 1980, 45, 1847.

^{507. (}a) Birch, A.J. Quart. Rev. (London), 1950, 4, 69; (b) Birch, A.J.; Smith, H. Ibid. 1958, 12, 17; (c) Watt, G.W. Chem. Rev. 1950, 46, 317; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-11; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 94-95.

^{508.} Donohoe, T.J.; House, D. J. Org. Chem. 2002, 67, 5015.



This leads to the functional group transforms:

$$\bigcirc OR \ \square \ \square \ OR \$$

There are a wide variety of synthetic applications of this chemistry, making it one of the more useful reactions in organic chemistry (sec. 10.5.B.vi). Partially reduced bicyclic and tricyclic aromatic derivatives⁵⁰⁹ can be formed by this method. It is also possible to reduce anisole derivatives to give cyclohexenone derivatives.

An example is the Birch reduction of methoxybenzene **514**, taken from a synthesis of periplanone MeO₂C C by Saicic and co-workers, which gave the non-conjugated cyclohexenone **515**, in 46% yield



after alkylation with allyl bromide.⁵¹⁰ In some cases, Birch reduction of anisole derivatives followed by treatment with acid, gives the conjugated cyclohexenone derivatives. In a synthesis of aeruginosin 298-A by Bonjoch and co-workers, Birch reduction of **516** gave **517**.⁵¹¹ Subsequent treatment with aqueous HCl gave **518**, but an intramolecular conjugate addition (sec. 9.) led to **519** as the final product in good yield. Note that it is possible to prevent the double bond of the initially formed vinyl ether from migrating into conjugation,⁵¹²



^{509.} Schultz, A.G.; Wang, A. J. Org. Chem. 1996, 61, 4857.

- 510. Ivkovic, A.; Matovic, R.; Saicic, R.N. Org. Lett. 2004, 6, 1221.
- 511. Valls, N.; López-Canet, M.; Vallribera, M.; Bonjoch, J. Chem. Eur. J. 2001, 7, 3446.
- 512. Kasturi, T.R.; Thomas, M. Indian J. Chem. 1972, 10, 777.

if hydrolysis is done under very mild conditions. Treatment with oxalic acid $[(CO_2H)_2]$ is commonly used for this purpose. Reduction of anisole derivatives is an important route to cyclohexenone derivatives and the functional group transformation is



One of the more interesting synthetic features of the Birch reduction is the ability to alkylate the carbanionic intermediate generated by the electron-transfer reaction, as in the synthesis of **515**. In another example, taken from a synthesis of plueromutilin,⁵¹³ Zard and co-workers converted **520** to **521** in 72% yield using a Birch reduction and trapping the anion intermediate with the alkyl halide shown.⁵¹³



As mentioned briefly above, Birch reduction is an important method for reducing heterocyclic aromatic rings. Although Birch reduction of unsubstituted pyrroles tends to give poor yields, reduction of the *N*-Boc derivatives can give quite good yields,⁵¹⁴ and reduction of pyridine rings to the piperidine derivative has been reported in low yield.⁵¹⁵ Partial reduction of a furan ring is also possible, as observed in the synthesis of secosyrin 1 by Donohoe and co-workers,⁵¹⁶ in which reduction of **522** led to a 68% yield of **523** (>20:1 dr) after reaction of the initially formed anion with the benzylic bromide shown.



4.9.F. The Benkeser Reduction

Lithium and sodium are the most commonly used metals in metal reductions, but Benkeser and co-workers developed the use of calcium in amines. In the initial work, naphthalene was reduced to an 80:20 mixture of Δ^9 -octalin (524) and $\Delta^{1(9)}$ -octalin (525) with lithium in

^{513.} Bacqué, E.; Pautrat, F.; Zard, S.Z. Org. Lett. 2003, 5, 325.

^{514.} For an example taken from a synthesis of the glycosidase inhibitor (2*R*,5*R*)-bis(hydroxymethyl)-3(*R*),4(*R*) dihydroxy-pyrrolidine (DMDP), see Donohoe, T.J.; Headley, C.E.; Cousins, R.P.C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999.

^{515.} Donohoe, T.J.; Guyo, P.M. J. Org. Chem. 1996, 61, 7664.

^{516.} Donohoe, T.J.; Fisher, J.W.; Edwards, P.J. Org. Lett. 2004, 6, 465.

diethylamine-dimethylamine.⁵¹⁷ Replacing lithium with calcium gave a 77:23 mixture of **524** and **525** in 92% yield.^{518,519} This method has come to be called the **Benkeser reduction**,⁵²⁰ and it is a useful modification because Birch reductions with sodium are difficult when run on kilogram scale, whereas the Benkeser reduction can give better yields of products. Addition of the proton source *tert*-butanol allows reduction of benzene rings to stop at the diene stage, which is useful for Birch reduction of aromatic rings.⁵²¹ Reduction of anisole with calcium under these conditions gave 86% of **510**, in addition to minor amounts of other reduction products.



Just as lithium and sodium can be used in low molecular weight amines for reduction of alkynes,⁵²² calcium is an effective reducing agent in amine solvents. Reaction of 2-nonyne with a calcium-methylamine-ethylenediamine mixture gave 87% yield of an 86:8:4 mixture of *trans*-2-nonene/*trans*-3-nonene/*trans*-4-nonene, the latter two products arising by bond isomerization.⁵²³

This reagent is also effective for reduction of epoxides. Lithium aluminum hydride reduction of **526** was very sluggish and required refluxing in *N*-methylmorpholine to obtain an 84% yield of **527**. Along with **527**, 16% of the rearranged alcohol **528** was isolated.⁵²⁴ Brown showed that reduction with lithium in diethylamine gave 64% of **527** and 35% of **528** after addition of **526** to the amine solution after one minute.⁵²⁵ If **526** was added after five minutes, however, only 10% of **527** and 3% of **529** was obtained along with unreacted starting material.⁵²⁶ When lithium was used with ethylenediamine, 87% of a 99.3:0.2:0.5 mixture of **527/528/529** was obtained.⁵²⁶ Benkeser showed that reduction of **526** with calcium in ethylenediamine gave an 89% conversion to **527** at ambient temperatures.⁵²⁶ This method is preferred for reduction of epoxides when LiAlH₄ fails or reacts very slowly.

- 517. Kaiser, E.M.; Benkeser, R.A. Org. Synth. Coll. Vol. 6 1988, 852.
- 518. Benkeser, R.A.; Kang, J. J. Org. Chem. 1979, 44, 3737.

- 520. The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-8.
- 521. Benkeser, R.A.; Laugal, J.A.; Rappa, A. Tetrahedron Lett. 1984, 25, 2089.
- 522. (a) Campbell, K.N.; Eby, L.T. J. Am. Chem. Soc. 1941, 63, 216, 2683; (b) Reference 489; (c) Benkeser, R.A.; Schroll, G.; Sauve, D.M. Ibid. 1955, 77, 3378.
- 523. Benkeser, R.A.; Belmonte, F.G. J. Org. Chem. 1984, 49, 1662.
- 524. Kwart, H.; Takeshita, T. J. Org. Chem. 1963, 28, 670.
- 525. Brown, H.C.; Ikegami, S.; Kawakami, J.H. J. Org. Chem. 1970, 35, 3243.
- 526. Benkeser, R.A.; Rappa, A.; Wolsieffer, L.A. J. Org. Chem. 1986, 51, 3391.

^{519.} Benkeser, R.A.; Belmonte, F.G.; Kang, J. J. Org. Chem. 1983, 48, 2796; (b) Benkeser, R.A.; Belmonte, F.G.; Yang, J. Synth. Commun. 1983, 13, 1103.



4.9.G. Reduction with Zinc

Zinc is an important metal for reduction of organic molecules,⁵²⁷ and zinc dust in acetic acid or HCl^{528} is probably the most common reagent. Zinc in acetic acid is a very effective reagent for reduction of α -haloketones, as in Deprés, Greene, and co-worker's synthesis of bakkenolide A^{529} where dichloride **530** was converted to **531** in 63% yield. Alkyl bromides and chlorides react with zinc and acetic acid very slowly when the halogen is *not* conjugated to a carbonyl. Reduction of primary iodides is relatively fast, and this method is commonly used to insert methyl groups into a synthetic target.⁵³⁰ Another reaction is observed when a molecule contains two halogen atoms on adjacent carbon atoms (a vicinal dihalide). Reductive dehalogenation to the alkene is a useful process, as seen in the Inoue, Hirama, and Sato synthesis of merrilactone A in which vicinal dichloride **532** was converted to **533**.⁵³¹ Similar eliminations are observed when sodium and ammonia⁵³² or a zinc-titanium tetrachloride (TiCl₄) reagent was used.⁵³³



Zinc in acetic acid leads to 1,4-reduction of conjugated ketones such as 534,⁵³⁴ in this case giving the saturated ketone 535 in Danishefsky and Mantlo's synthetic studies on calicheamicin. This conjugated system is quite sensitive, but Zn/AcOH gave > 82% of the desired conjugate reduction product 535.

- 528. Reference 15, pp 1276-1284.
- 529. Brocksom, T.J.; Coelho, F.; Deprés, J.-P.; Greene, A.E.; de Lima, M.E.F.; Hamelin, O.; Hartmann, B.; Kanazawa, A.M.; Wang, Y.J. Am. Chem. Soc. 2002, 124, 15313.
- 530. Yamada, K.; Nagase, H.; Hayakawa, Y.; Aoki, K.; Hirata, Y. Tetrahedron Lett. 1973, 4963.
- 531. Inoue, M.; Sato, T.; Hirama, M. J. Am. Chem. Soc. 2003, 125, 10772.
- 532. Schubert, W.M.; Rabinovitch, B.S.; Larson, N.R.; Sims, V.A. J. Am. Chem. Soc. 1952, 74, 4590.
- 533. Sato, F.; Akiyama, T.; Iida, K.; Sato, M. Synthesis 1982, 1025.
- 534. Mantlo, N.B.; Danishefsky, S.J. J. Org. Chem. 1989, 54, 2781.

^{527.} Reference 7, pp 28-29.



Clemmensen reduction⁵³⁵ is the classical method for removing a ketone carbonyl via reaction with zinc amalgam (Zn/Hg) in HCl. An example is taken from a synthesis of mutisianthol by Ferraz and co-workers,⁵³⁶ in which the ketone unit in **536** was removed with zinc-amalgam in HCl to give **537**, in 68% yield. Another use of this reduction is for removal of a hydroxyl group from an acyloin such as **538** (sec. 13.8.E), to give cyclodecanone, **539**.⁵³⁷ Cram introduced a useful modification of this latter reduction. Reaction of the acyloin **540** with acidic zinc chloride, in the presence of 1,3-propanedithiol,⁵³⁸ reduced the alcohol via hydrogenolysis, and converted the carbonyl to a dithioketal (**541**) in 82% yield. The dithiane moiety was reduced to **542** in 85% yield with Raney nickel in Cram's example, but hydrolysis to the ketone with aqueous mercuric salts is also possible (sec. 7.3.B.ii).



It was previously mentioned that zinc reduces alkynes to alkenes. Näf showed that reduction of the conjugated alkyne (543) to the conjugated cis alkene (in 544) occurred with zinc in the presence of potassium cyanide (KCN). This reduction was not possible by hydrogenation

- 537. Prelog, V.; Schenker, K.; Günthard, H.H. Helv. Chim. Acta 1952, 35, 1598.
- 538. Cram, D.J.; Cordon, M. J. Am. Chem. Soc. 1955, 77, 1810.

^{535. (}a) Clemmensen, E. Berichte 1913, 46, 1837; (b) Vedejs, E. Org React. 1975, 22, 401; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-18; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 160-161.

^{536.} Ferraz, H.M.C.; Aguilr, A.M.; Silva Jr., L.F. Tetrahedron 2003, 59, 5817.

with a Lindlar catalyst, due to the poor selectivity for reaction with only the alkyne without reduction of any alkenes.⁵³⁹ The yields obtained by zinc reduction were not always reproducible, however.^{539b}

$$\underbrace{\overset{n-C_5H_{11}}{\underbrace{\operatorname{Zn}^\circ,\operatorname{KCN},\operatorname{C_3H_7OH}}}_{5^\circ\mathrm{C}}}_{\mathbf{544}}$$

The functional group transforms available with zinc are

$$\overset{R}{\underset{R}{\succ}} H \overset{R}{\underset{R}{\succ}} \overset{R}{\underset{R}{\rightarrow}} Br \qquad \overset{R}{=} \overset{\Gamma}{\overset{O}} \overset{R}{\underset{R}{=}} \overset{\Gamma}{\overset{O}} \overset{R}{\underset{R}{=}} \overset{\Gamma}{\overset{O}} \overset{R}{\underset{R}{\rightarrow}} \overset{R}{\underset{OH}{=}} \overset{R}{\underset{R}{\leftarrow}} \overset{R}{\underset{H}{\leftarrow}} \overset{R}{\underset{R}{\leftarrow}} \overset{R}{\underset{R}{{\leftarrow}} \overset{R}{\underset{R}{{\leftarrow}} \overset{R}{\underset{R}{\leftarrow}} \overset{R}{$$

4.9.H. Reduction with Tin and Tin Compounds

Tin metal is used sparingly as a reducing metal in modern organic synthesis, but tin derivatives such as tributytin hydride are common. Aldehydes, for example, are readily reduced with tributyltin hydride (Bu₃SnH) in aqueous media. An example is the reduction of 2-naphthaldehyde to the alcohol (**392**) in 93% yield, in refluxing methanol.⁵⁴⁰ When this reaction was done in water, an 85% yield of **392** was obtained.



For the reduction of other functional groups with tin or a derivative, heating with HCl is often required and in such cases other reducing methods are usually more convenient. Typical applications include reduction of acyloins and aromatic nitro compounds.⁵⁴¹ A classical use of tin that is still used occasionally is the so-called **Stephen reduction**, where a nitrile is converted to the corresponding aldehyde.⁵⁴² An example is the reduction of lauronitrile (**545**) to give lauraldehyde (**548**), when treated with a stannous chloride (SnCl₂) solution that is saturated with anhydrous HCl.⁵⁴³ The reaction proceeds by initial addition of HCl to the nitrile to give

543. (a) Lieber, E. J. Am. Chem. Soc. 1949, 71, 2862; (b) Knight, J.A.; Zook, H.D. Ibid. 1952, 74, 4560.

⁽a) Näf, F.; Decorzant, R.; Thommen, W.; Wilhalm, B.; Ohloff, G. Helv. Chim. Acta 1975, 58, 1016; (b) Fieser, L.F.; Fieser, M. Reagents for Organic Synthesis Vol. 6, Wiley, New York 1977, p674.

^{540.} Kamiura, K.; Wada, M. Tetrahedron Lett. 1999, 40, 9059.

^{541. (}a) Reference 7, pp 29-30; (b) Reference 15, p1168.

^{542. (}a) Stephen, H. J. Chem. Soc. 1925, 127, 1874; (b) Ferguson, L.N. Chem. Rev. 1946, 38, 227 (see p243);
(c) Mosettig, E. Org. React. 1954, 8, 218 (see pp 246-252).

546. This intermediate is reduced by stannous chloride to give **547** and $SnCl_2$ is converted to tin tetrachloride (SnCl₄). Subsequent treatment with aqueous HCl hydrolyzes imine **547** to aldehyde **548** in 73% overall yield. Stannous bromide (SnBr₂) often gives better yields of aldehyde than stannous chloride. Most aromatic nitriles give good yields of the aromatic aldehyde.⁵⁴⁴

As mentioned, tin derivatives are typically used more often than tin metal in synthetic applications. Trialkyltin hydrides, for example, are important for radical hydrogen transfer in reductions of alkyl, alkenyl, and aryl halides (see sec. 13.5.D).⁵⁴⁵ In an example, taken from Marino and co-worker's⁵⁴⁶ synthesis of (+)-aspidospermidine, the CCl₂ moiety of **549** was reduced to -CH₂- (see **550**) in 92% yield using tri-*n*-butyltin hydride. Corey and Suggs showed that this reaction can be made catalytic,⁵⁴⁷ when the tin hydride is generated *in situ* by photolysis of a mixture of trimethyltin chloride and ethanolic sodium borohydride. Tributyltin chloride can be used as well. The reaction is not restricted to aliphatic derivatives, and vinyl bromides are reduced to the alkene with tin hydride.⁵⁴⁸ One of the more common uses of tin hydride is as a hydrogen transfer agent in radical cyclization reactions⁵⁴⁹ (sec. 13.7). A number of other functional group reductions have been reported with Bu₃SnH, including reduction of nitro groups⁵⁵⁰ and azido groups⁵⁵¹ to amines.



A variation of the tributyltin hydride reduction is available that can be applied to alcohols. The alcohol is converted to a thionocarbonate and then reduced with Bu₃SnH and AIBN, which circumvents the need for conversion of the alcohol to a halide. This transformation is known

- 545. Curran, D.P. Synthesis 1988, 417, 489.
- 546. Marino, J.P.; Rubio, M.B.; Cao, G.; de Dios, A. J. Am. Chem. 2002, 124, 13398.
- 547. Corey, E.J.; Suggs, J.W. J. Org. Chem. 1975, 40, 2554.
- 548. For an example taken from a synthesis of cordiachromene, see Bouzbouz, S.; Gougon, J.-Y.; Deplanne, J.; Kirschleger, B. *Eur. J. Org. Chem.* **2000**, 3223.
- 549. Kraus, G.A.; Hon, Y.-S. J. Org. Chem. 1985, 50, 4605.
- 550. Brakta, M.; Lhoste, P.; Sinou, D. J. Org. Chem. 1989, 54, 1890.
- 551. Wasserman, H.H.; Brunner, R.K.; Buynak, J.D.; Carter, C.G.; Oku, T.; Robinson, R.P. J. Am. Chem. Soc. 1985, 107, 519.

^{544.} Slotta, K.H.; Kethur, R. Berichte 1938, 71, 335.

as the **Barton deoxygenation** or the **Barton-McCombie reaction**.⁵⁵² A synthetic example is the reduction of the OH unit in 551 to give 552 in >90% yield, from Mander and Thomson's synthesis of sordaricin.⁵⁵³ In the general reaction, treatment with sodium hydride and then



formation of a xanthate ester tributyltin hydride and AIBN to give reductive cleavage of the

C-O bond. Fu and co-workers have shown that the reaction can be done in the presence of polymethylhydrosiloxane using a catalytic amount of tributyltin hydride.⁵⁵⁴

4.9. Reduction with Aluminum and Aluminum Compounds

The Meerwein-Ponndorf-Verley reduction is a classical reaction that uses metals,⁵⁵⁵ and it is the reverse of the **Oppenauer oxidation** discussed in Section 3.2.E.ii.⁵⁵⁶ The mechanistic details of this reversible reaction are presented in that section.⁵⁵⁷ The major difference between reduction or oxidation is the use of an alcohol solvent rather than a ketone solvent (usually 2-propanol rather than acetone). A ketone is treated with an aluminum alkoxide such as triisopropoxyaluminum, in the presence of a hydrogen-donating solvent such as 2-propanol. Refluxing conditions are usually required to initiate transfer of the hydrogen to the ketone, reducing it and generating acetone from 2-propanol. An uncatalyzed version of this reaction was reported to proceed in supercritical fluids.⁵⁵⁸ A synthetic example is the reduction of 553 to give an 84% yield of the anti-diastereomer 554, along with 15% of the syn-alcohol in Manaviazar, Hale and co-worker's synthesis of bryostatin 7.559

^{552. (}a) Barton, D.H.R.; McCombie, S.W. J. Chem. Soc. Perkin Trans. 1 1975, 1574; Phenyl thionocarbonates were first used by (b) Robins, M.J.; Wilson, J.S.; Hanssla, F. J. Am. Chem. Soc. 1983, 105, 4059; (c) Robins, M.J.; Wilson, J.S. J. Am. Chem. Soc. 1981, 103, 932; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-6; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 68-69.

^{553.} Mander, L.N.; Thomson, R.J. Org. Lett. 2003, 5, 1321.

^{554.} Lopez, R.M.; Hays, D.S.; Fu, G.C. J. Am. Chem. Soc. 1997, 119, 6949.

^{555. (}a) de Graauw, C.F.; Peters, J.A.; van Bekkum, H.; Huskens, J.; Synthesis 1994, 1007; (b) Wilds, A.L. Org. React. 1947, 2, 178; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-59; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 418-419.

^{556.} Djerassi, C. Org. React. 1951, 6, 207.

^{557.} Also see Liu, Y.-C.; Ko, B.-T.; Huang, B.-H.; Lin, C.-C. Organometallics 2002, 21, 2066.

^{558.} Sominsky, L.; Rozental, E.; Gottlieb, H.; Gedanken, A.; Hoz, S. J. Org. Chem. 2004, 69, 1492.

^{559. (}a) Manaviazar, S.; Frigerio, M.; Bhatia, G.S.; Hummersone, M.G.; Aliev, A.E.; Hale, K.J. Org. Lett. 2006, 8, 4477. For a comparison of Meerwein-Pondorff-Verley reduction versus LiAlH4 in a synthesis of dihydrocrinine, see (b) Irie, H.; Uyeo, S.; Yoshitake, A. J. Chem. Soc. C 1968, 1802; (c) Idem J. Chem. Soc. Chem. Commun. 1966, 635.



Aluminum amalgam (Al/Hg) is also a useful reagent that is commonly used for hydrogenolysis of sulfur compounds.⁵⁶⁰ Reduction of sulfoxides is an important application,⁵⁶¹ as is reduction of sulfones. Aluminum amalgam reduced the α -phenylsulfonyl moiety in **555** to give lactone **556** in 68% yield, for example.⁵⁶² Aluminum amalgam has also been used for reduction of nitro compounds to the amine,⁵⁶³ and reduction of azides to the amine.⁵⁶⁴



The functional group transforms for reductions with aluminum compounds are



4.9.J. Electrolytic Reductions

The standard reduction potential⁶ of alkali metals involves a single electron transfer.⁵⁶⁵ Electron transfer can also be done in an electrolytic cell as described in Section 3.1. Electrolysis of acetone is an example where an electron is transferred to the carbonyl, generating a radical anion (a ketyl, see sec. 4.9.B). We have seen that the fate of these reactive species depends on the solvent, and in the case of electrolysis, whether or not the electrode potential allows an additional electron transfer and what reactive species may be present in the reaction medium.

564. (a) Woodward, R.B.; Heusler, K.; Gosteli, J.; Naegeli, P.; Oppolzer, W.; Ramage, R.; Ranganathan, S.; Vorbrüggen, H. J. Am. Chem. Soc. 1966, 88, 852; (b) Woodward, R.B. Science 1966, 153, 487.

^{560.} Reference 15, pp 20-22.

^{561.} Vig, O.P.; Sharma, S.D.; Matta, K.L.; Sehgal, J.M. J. Indian Chem. Soc. 1971, 48, 993.

^{562.} Yamamoto, M.; Takemori, T.; Iwasa, S.; Kohmoto, S.; Yamada, K. J. Org. Chem. 1989, 54, 1757.

^{563.} Fleming, I. in *New Trends in Natural Product Chemistry 1986*, Rahman, A.W.; LeQuesne, P.W. (Ed.), Elsevier, Amsterdam **1986**, p83.

^{565.} Reference 6, pp 24-25.

There are at least two major types of reaction products available to the ketyl as introduced in Section 4.9.B. It can undergo radical coupling, or it can remove a hydrogen atom from an acidic solvent (such as ethanol or ammonia) and be reduced. The radical coupling of acetone described is formally known as **pinacol coupling** (the **pinacol reduction**)⁵⁶⁶,484a and is described in Section 13.8.D.

Aldehydes usually undergo reductive dimerization upon electrolysis, as in the formation of 4,5-octanediol in 55% yield from butanal.⁵⁶⁷ Small chain aldehydes (such as acetaldehyde) give significant amounts of reduction to the alcohol, but the proportion of dimer increases as the chain length increases. The increased amount of dimer is probably due to increased hydration of the small aldehydes and the alcohol products.

The electrochemical properties of many functional groups have been described in reviews by Steckhan,⁵⁶⁸ Degner (industrial uses of electrochemistry),⁵⁶⁹ Kariv-Miller,⁵⁷⁰ and by Feoktistov.⁵⁷¹ Synthetic applications of anodic electrochemistry have also been reviewed.⁵⁷² There are interesting differences between dissolving metal reductions (secs. 4.9.B-G) and electrochemical reactions. By controlling the reduction potential, the nature of the electrode and the reaction medium, cyclohexanone can be reduced to cyclohexanol (sec. 4.9.B) or converted to the 1,2-diol (**557**) via pinacol coupling.⁵⁷³ Presumably, the more concentrated conditions favor formation of cyclohexanol via reduction of the carbanion. More dilute solutions appear to favor the radical, with reductive dimerization to **557**. More important to this process, however, is the difference in reduction potential (–2.95 versus –2.70 V), and the transfer of two Faradays per mole in the former reaction, and four Faradays per mole in the latter.

Coupling between two different species is possible under some conditions, particularly when an aryl halide is one of the partners. When indole was treated with 4-chloropyridine, for example, under electrolytic conditions, a 60% yield of **558** was obtained⁵⁷⁴ when 4,4'-bipyridyl (bpy) was used as a redox mediator.

Reduction of alkynes to the trans-alkene proceeds via a radical anion such as **479** (see sec. 4.9.C), and is virtually identical to similar reduction involving alkali metals (sec. 4.9.C). Electrolytic

- 572. Moeller, K.D. Tetrahedron 2000, 56, 9527.
- 573. Kariv-Miller, E.; Mahachi, T.J. J. Org. Chem. 1986, 51, 1041.
- 574. Chahma, M.; Combellas, C.; Thiébault, A. Synthesis 1994, 366.

^{566.} Schreibman, A.A.P. Tetrahedron Lett. 1970, 4271.

^{567.} Khomyakov, V.G.; Tomilov, A.P.; Soldatov, B.G. Elektrokhimiya, 1969, 5,853 [Chem. Abstr. 71: 108403p1969].

^{568.} Steckhan, E. in *Electrochemistry I*, Steckhan, E. (Ed.), Springer-Verlag, Berlin, 1987, pp 31-49.

^{569.} Degner, D. in *Electrochemistry III*, Steckhan, E. (Ed.), Springer-Verlag, Berlin, 1988, pp 40-91.

^{570.} Kariv-Miller, E.; Palcut, R.I.; Lehman, G.K. in *Electrochemistry III*, Steckhan, E. (Ed.), Springer-Verlag, Berlin, *1988*, pp 97-130.

^{571.} Feoktistov, L.G.; Lund, H.; Eberson, L.; Horner, L. *Organic Electrochemistry*, Baizer, M.M. (Ed.), Marcel Dekker, New York, *1973*, pp 355-366.

reduction of but-2-yn-1,4-diol (**559**) gave an 82% yield of (*E*)-but-2-en-1,4-diol (**560**).⁵⁷⁵ Electrolytic reduction of alkynes is sensitive to reaction conditions. Although the trans alkene is usually



formed, Hudlicky cited Campbell and Young's work⁵⁷⁶ in which electrolysis of alkynes (in 95% EtOH + H_2SO_4) on a spongy nickel cathode gave 65-80% of the cis alkene. Similar reaction in a methylamine solution containing LiCl gave the trans alkene. The sensitivity to reaction conditions is apparent in the reduction of conjugated carbonyl systems, which are reduced electrolytically to give the 1,4-reduction product.⁵⁷⁷ Note that electrolysis of cyclohexenone did not give reduction products but rather reductive coupling products. A difference between electrolysis and dissolving metal reductions is the ability to reduce simple double bonds, as in the electrolytic reduction of 1,5-cyclooctadiene to cyclooctene.⁵⁷⁸ Another difference is noted in the electrolysis of conjugated acid derivatives, which give reductive coupling products.

Electrolysis of conjugated ketones generates a radical anion by addition of an electron to the conjugated system, but dimerization usually occurs by coupling at the end of the conjugated system.⁵⁷⁹ Such dimerizations can occur even with significant steric hindrance at the terminal alkene carbon.⁵⁸⁰ Conjugated nitriles and esters show a preference for coupling at the end of the conjugated system. 2-Methylpropenenitrile,⁵⁸¹ for example, was dimerized in high yield to 2,5-dimethyladiponitrile and ethyl acrylate was coupled to an aldehyde to give a γ-hydroxy ester (which cyclized to the lactone).⁵⁸²



Electrolytic conditions can be used to achieve Birch reductions (sec. 4.9.E),⁵⁸³ as in the reduction of 2-methoxynaphthalene (561) to give 562 in 95% yield.⁵⁸⁴

Electrolysis of heterocycles leads to interesting reduction products. Pyridine, for example,

^{575.} Horner, L.; Röder, H. Liebigs Ann. Chem. 1969, 723, 11.

^{576. (}a) Campbell, K.N.; Young, E.E. J. Am. Chem. Soc. 1943, 65, 965; (b) Reference 7, p 45.

^{577.} Hull, D.A.; Heiney, R.E. (Eli Lilly) US 4 082 627 [Chem. Abstr. 89: 119769k 1978].

^{578.} Reference 568, citation 373 therein.

^{579. (}a) Brillas, E.; Ortiz, A. *Electrochem. Acta* 1985, 30, 1185; (b) see Zimmer, J.P.; Richards, J.A.; Turner, J.C.; Evans, D.H. Anal. Chem. 1971, 43, 1000.

^{580.} Bowers, K.W.; Giese, R.W.; Grimshaw, J.; House, H.O.; Kolodny, N.H.; Kronberger, K.; Roe, D.K. J. Am. Chem. Soc. 1970, 92, 2783.

^{581. (}a) Asahi Chem. J 59 219 485 [Chem. Abstr. 102: 228324a 1985]; (b) Idem J 60 050 190 [Chem. Abstr. 103: 61495g 1985]; (c) Idem J 60 052 587 [Chem. Abstr. 103: 131244a 1985].

^{582. (}a) Asahi Chem. J 57 108 274 [Chem. Abstr. 97: 171368k 1982]; (b) Idem J 58 207 383 [Chem. Abstr. 100: 164348e,d 1984].

^{583. (}a) Asahara, T.; Senö, M.; Kaneko, H. Bull. Chem. Soc. Jpn. 1968, 41, 2985; (b) Misono, A.; Osa, T.; Yamagishi, T. Ibid. 1968, 41, 2921.

^{584.} Skatelz, D.H.O. (Hoechst) DE 2 618 276 [Chem. Abstr. 88: 62213x 1978]

gave the reductive dimerization product **563** but air oxidation rapidly converted it to **564**.⁵⁸⁵ As well as partial reduction, heteroaromatic rings can be completely reduced, as in the conversion of **565** to **566** in 95% yield in glacial acetic acid.⁵⁸⁶



Electrochemical processes can be used for the reduction of many other functional groups. Halogen is removed, as in the reduction of 6-chloro-1-hexene to 1-hexene in 23% yield (in DMF).⁵⁸⁷ Aryl halides are similarly reduced electrochemically. 2-Chloroaniline, for example, was reduced to aniline in 85% yield.⁵⁸⁸ If the electrodes and solvent are changed, reductive coupling can occur.⁵⁸⁹ Elimination is possible in some cases.⁵⁹⁰ Epoxides are opened electrochemically, and hydrogen is often delivered to the more substituted carbon, as in the quantitative conversion of **567** to **568**.⁵⁹¹ Azides are reduced to the amine.⁵⁹²



Nitro compounds are reduced to the corresponding amine. Unlike hydride reductions, both alkyl nitro compounds [2-methyl-2-nitro-1,3-propanediol was reduced to 1-amino-2-methyl-1,3-propanediol in 95% yield)]⁵⁹³ and aromatic nitro derivatives [nitrobenzene was reduced to aniline with $Ti(SO_4)_3$ in sulfuric acid and cetyltrimethylammonium bromide] are electrolytically

- 589. Baldwin, M.M.; Wyant, R.E. (Battelle Dev. Corp) US 4 434 032 [Chem. Abstr. 100: 164313; 1984].
- 590. Torii, S.; Tanaka, H.; Sasaoka, M.; Kameyama, Y. (Otsuka Chem. Co.) DE 3 507 592 [*Chem. Abstr. 104*: 148628x **1986**].

^{585.} Asahi Chem. Jpn. JP 81 112,488 1981 [Chem. Abstr. 96: 59966e 1982].

^{586. (}a) Hannebaum, H.; Nohe, H. Müller, H.R. (BASF) DE 2 403 446 [*Chem. Abstr. 83*: 210783x 1975]; (b) Nohe, H.; Hannebaum, H. (BASF) DE 2 658 951 [*Chem. Abstr. 89*: 109092v 1978]; (c) Kormasch, V.V.; Kormachev, V.V.; Trentovskaya, L.K.; Abramov, I.A.; Shevnitsyn, L.S.; Danilov, S.D. SU 844 616, [*Chem. Abstr. 95*: 150443x 1981].

^{587.} Lund, H.; Michel, M.A.; Simonet, J. Acta Chem. Scand. 1975, 29B, 217.

^{588.} Seiler, J.N.; Strigham, R.R. (Dow) US 3 677 916 [Chem. Abstr. 78: 10920z 1973].

^{591.} Kamernitskii, A.V.; Reshetova, I.G.; Chernoburova, E.I.; Mairanovskii, S.G.; Lisitsina, N.K. *Izv. Akad. Nauk. SSSR Ser. Khim* **1984**, 1901 (Engl. p 1736).

^{592.} Kuwabata, S.; Tanaka, K.; Tanaka, T. Inorg. Chem. 1986, 25, 1691.

^{593.} Rignon, M.; Catonne, J.C.; Denisard, F.; Malafosse, J.EP198722 [FR2, 577, 242 Chem. Abstr. 108: 111810g 1988].



reduced.⁵⁹⁴ If conditions are modified, reductive coupling can give azoxy compounds such as **569** (from **570**)⁵⁹⁵ or diazo compounds.⁵⁹⁶ A variety of acid derivatives are reduced under electrochemical conditions, including nitriles (to amines),⁵⁹⁷ acids

(to alcohols),^{598,599} esters (to alcohols),⁶⁰⁰ and amides (to alcohols).⁶⁰¹ It is possible to selectively reduce a cyclic imide to a lactam.⁶⁰²

4.10. NONMETALLIC REDUCING AGENTS

There are several methods for reducing organic functional groups that use nonmetallic reagents. The mechanism of reduction varies with each reagent, and each has a rather specific and useful application. This section is presented as a survey of these methods and is not intended as an indepth analysis. The intent is to offer alternatives for the reduction of functional groups when more traditional methods fail.

4.10.A. Reduction with Hydrazine (Wolff-Kishner)

When a carbonyl group must be removed from a molecule, the acidic conditions of the **Clemmensen reduction** (sec. 4.9.G) are not always compatible with other functional groups that may be present. An alternative method of reduction was developed in basic media that relied on the reaction of carbonyls with hydrazine to form a hydrazone. In the presence of base, a hydrazone anion intermediate (sec. 9.4.F) can be formed that removes a proton from the acidic solvent leading to reduction. This process has been termed the **Wolff-Kishner**

^{594.} Noel, M.; Anatharaman, P.N.; Udupa, H.U.K. Electrochem. Acta 1980, 25, 1083.

^{595.} deGroot, H.; van de Henvel, E.; Barendrecht, E., Janssen L.J.J. DE 3 020 846 [Chem. Abstr. 94: 54934s 1981].

 ^{596. (}a) Kovsman, E.P.; Freidlin, G.N.; Soldatov, B.G.; Motsak, G.V. SU 415 969, 484 745 and 533 590 [Chem. Abstr. 86: 23589p, 23588n and 120987z 1977]; (b) Idem SU 655 701 [Chem. Abstr. 91: 20129f 1979].

^{597. (}a) Kirilyus, I.V.; Murzatova, G.K.; Frangulyan, G.A.; Polievktov, M.K. (AS Kaza Chem. Metall.) SU 777 024 [*Chem. Abstr.* 94: 174610e 1981]; (b) also see Toomey, J.E. (Reilly Tar & Chemical Corp.) US 4 482 437 [*Chem. Abstr.* 102: 53 067h 1985].

^{598.} Takenaka, S.; Shimakawa, C. (Mitsui Toatsu Chem.) J 60 243 293 and J 60 234 987 [*Chem. Abstr. 104*: 138283s and 98055k **1986**].

^{599.} Beck, F.; Jäger, P.; Guthke, H. (BASF) DE 1 950 282 [Chem. Abstr. 74: 140980x 1971].

^{600.} Horner, L.; Skaletz, D.H.; Hönl, H. (Hoechst) DE 2 428 878 [Chem. Abstr. 84: 105228t 1976].

^{601. (}a) Heitz, E.; Kaiser, U. (Dechema), DE 2 301 032, [*Chem. Abstr. 81*: 130200y **1974**]; (b) Toomey, J.E. (Reily Tar and Chemical Corp.), EP 189 678 [*Chem. Abstr.* 105: 215760v **1986**].

^{602. (}a) Pliva Pharm J 77 116 464 [*Chem. Abstr.* 88: 152418x 1978]; (b) Crnic, Z.; Djokic, S.; Gaspert, B.; Vajtner, Z.; Maasboel, A. (Pliva Corp.), AU 355 013 [*Chem. Abstr.* 93: 8010u 1980].

reduction.⁶⁰³ There are several modifications of this procedure, including isolation of the hydrazone, and using an alkoxide base.⁶⁰⁴ Perhaps the most important change in this reaction is the **Huang-Minlon modification**, which uses refluxing diethylene glycol as the solvent

and has been shown to be much more efficient for this transformation.⁶⁰⁵ Reduction of the aldehyde unit in **571** using this modification gave **572** in 57% yield in Taber and co-worker's synthesis



of (–)-calicoferol B.⁶⁰⁶ Alternatives are available. Hydrazine hydrochloride (N₂H₄•HCl) has been shown to be effective for the reduction of sterically hindered ketones.⁶⁰⁷ Hydrazine is also used to convert an alkyl phthalimide to an alkyl amine by replacing the H₂C-NR-CH₂ moiety with a O=C–NHNH–C=O unit, in what is often called the **Ing-Manske procedure**.⁶⁰⁸

There is an alternative to the Wolff-Kishner or Clemmensen reductions (Sec 4.9.G) of ketones and aldehydes. Reaction of a ketone or aldehyde with 1,3-propanedithiol, in the presence of a Lewis acid, gives the corresponding dithiane (see **573**; Sec 7.3.B.ii). Subsequent treatment with Raney nickel, usually in ethanol or methanol, leads to desulfurization, as shown. Dithiane, dithiolanes, or dithioketals or dithioacetals can be used in this transformation. An example is taken from Pu and Ma's synthesis of (–)-alkaloid 223A,⁶⁰⁹ in which **574** was converted to the dithiolane (**575**), and subsequent heating with Raney nickel and hydrogen in isopropanol gave the desulfurized product **576**. See section 8.6 for other reactions of sulfur compounds.



- 603. (a) Kishner, N. J. Russ. Phys. Chem. Soc. 1911, 43, 582; (b) Wolff, L. Annalen, 1912, 394, 86; (c) Todd, D. Org. React. 1948, 4, 378; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-103; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 704-705.
- 604. (a) Grudnon, M.F.; Henbest, H.B.; Scott, M.D. J. Chem. Soc. 1963, 1855; (b) Sobti, R.R.; Dev, S. Tetrahedron 1970, 26, 649.
- 605. (a) Huang-Minlon J. Am. Chem. Soc. 1946, 68, 2487; (b) Idem Ibid. 1949, 71, 3301.
- 606. Taber, D.F.; Jiang, Q.; Chen, B.; Zhang, W.; Campbell, C.L. J. Org. Chem. 2000. 67. 4821.
- 607. Nagata, W.; Itazaki, H. Chem. Ind. 1964, 1194.
- 608. Ing, H.R.; Manske, R.H.F. J. Chem. Soc. 1926, 2348.
- 609. Pu, X.; Ma, D. J. Org. Chem. 2003, 68, 4400.

The functional group transform for reduction with hydrazine or of the dithiane is

$_{R}^{R} \!$	\Box	$_{R}^{R} \succ 0$

4.10.B. Reduction with Diimide

Diimide (NH=NH) is a transient species generated by reaction of acids with potassium azodicarboxylate,⁶¹⁰ by thermolysis of anthracene-9,10-diimine,⁶¹¹ from hydrazine derivatives⁵⁵⁵ or tosylhydrazone.⁶¹² Diimide reduces isolated C=C units to the corresponding saturated derivatives (i.e., C=C \rightarrow –CH₂CH₂-).⁶¹³ It is known that diimide gives primarily cis reduction of alkenes⁶¹⁴ and *reduces symmetricall* π *bonds faster than polarized* π *bonds*.⁶¹⁵ Generation of diimide with potassium azodicarboxylate gave selective reduction at the least conjugated alkene in **577** to give **578** in 77% yield, an important intermediate in Corey and co-worker's synthesis of ovalicin.⁶¹⁶ The conjugated ketone and exocyclic epoxide were not reduced. In a synthesis of frondosin C, Ovaska and co-worker's reduced a single alkene unit in **579** to give **580** in 70% yield using diimide generated *in situ* from tosylhydrazine.⁶¹⁷ Corey showed that the course of a reduction with diimide could be altered by addition of cupric salts [such as cupric acetate, Cu(OAc)₂].⁶¹⁸ This new reagent is highly selective for the reduction of conjugated alkenes, with specificity for the less substituted double bond of the diene.⁶¹⁹



- 610. Adam, W.; Eggelte, H.J. J. Org. Chem. 1977, 42, 3987.
- 611. (a) Reference 7, pp 33-34; (b) Reference 15, pp 257-258.
- 612. For an example taken from the synthesis of aplyronines, see Marshall, J.A.; Johns, B.A. J. Org. Chem. 2000, 65, 1501.
- 613. See Reference 17, p 12.
- 614. (a) Hünig, S.; Müller, H.-R.; Thier, W. *Tetrahedron Lett.* **1961**, 353; (b) van Tamelen, E.E.; Timmons, R.J. *J. Am. Chem. Soc.* **1962**, *84*, 1067.
- 615. van Tamelen, E.E.; Dewey, R.S.; Lease, M.F.; Pirkle, W.H. J. Am. Chem. Soc. 1961, 83, 4302.
- 616. Corey, E.J.; Dittami, J.P. J. Am. Chem. Soc. 1985, 107, 256.
- 617. Li, X.; Kyne, R.E.; Ovaska, T.V. Org. Lett. 2006, 8, 5153.
- 618. (a) Corey, E.J.; Mock, W.L.; Pasto, D.J. *Tetrahedron Lett.* **1961**, 347; (b) Corey, E.J.; Hortmann, A.G. *J. Am. Chem. Soc.* **1965**, 87, 5736.
- 619. For an example, see Corey, E.J.; Yamamoto, H. J. Am. Chem. Soc. 1970, 92, 6636.

The functional group transform is



4.10.C. Reduction with Silanes (Hydrosilylation)

Alkyl silanes can be used for the reduction of carbonyls and alkenes. Methylcyclohexene was reduced to methylcyclohexane using a mixture of triethylsilane (Et₃SiH) and trifluoroacetic acid (CF₃CO₂H), in 72% yield.⁶²⁰ Under the same conditions, however, 1-pentene was not reduced. This reagent is often used for reduction of conjugated carbonyls, probably via formation of a silvl enolate (secs. 9.2, 9.3.B), as in the reduction of cyclohexenone to cyclohexanone in 85% yield with Ph₂SiH₂.⁶²¹ Transition metals such as ZnCl₂, rhodium derivatives or copper salts can be added to the silane to facilitate the reduction.⁶²² An example, taken from a synthesis of (+)-manoalide by Kocienski and co-workers, reduced the conjugated double bond in β -ionone (581) to give 582 in 90% yield using the two-step procedure shown.⁶²³ Conjugated aldehydes tend to give 1,2-reduction, as in the reduction of 3-phenyl-prop-(2E)-enal to 3-phenylprop-(2E)-en-1-ol in 95% yield.⁶²⁴ Another example of such selectivity is the reduction of the ketone unit in 2-bromo-1-phenylpropanone to give 2-bromo-1-phenyl-1-propanol in 70% yield.⁵⁷⁰ Non-conjugated ketones and aldehydes are reduced by silanes in acid media, as in the reaction of cyclohexanone with Et₃SiH and trifluoroacetic acid to give cyclohexanol in 74% yield.⁶²⁰ Ketones are usually reduced faster than epoxides.^{625,626} The use of a chiral additive gives asymmetric reduction with silanes. Reduction of acetophenone gave (R)-phenethyl alcohol in 99% yield and 84.2% ee, in the presence of **583**.⁶²⁷



Reductive cleavage of carbonyls or alcohols, analogous to the Wolff-Kishner or Clemmensen

621. Sharf, V.Z.; Freidlin, L.Kh.; Shekoyan, I.S.; Krutii, V.N. Bull. Akad. USSR Chem. 1977, 26, 995.

- 623. Pommier, A.; Stepanenko, V.; Jarowicki, K.; Kocienski, P.J. J. Org. Chem. 2003, 68, 4008.
- 624. Boyer, J.; Corriu, R.J.P.; Perz, R.; Réyé, C. J. Chem. Soc. Chem. Commun. 1981, 121.
- 625. Mullholland, Jr., R.L.; Chamberlin, A.R. J. Org. Chem. 1988, 53, 1082.
- 626. Salomon, R.G.; Sachinvala, N.D.; Raychaudhuri, S.R.; Miller, D.B. J. Am. Chem. Soc. 1984, 106, 2211.
- 627. Brunner, H.; Riepl, G.; Weitzer, H. Angew. Chem. Int. Ed. 1983, 22, 331.

^{620.} Kursanov, D.N.; Parnes, Z.N.; Bassova, G.I.; Loim, N.M.; Zdanovich, V.I. Tetrahedron 1967, 23, 2235.

^{622.} Ojima, I.; Kogure, T. Organometallics 1982, 1, 1390.

reduction, is illustrated by conversion of cyclohexanone to cyclohexane in 90% yield, 628 using a silane•BF₃ complex. Other modifications, such as addition of cesium fluoride, give reduction of an ester moiety. 629

The functional group transforms observed in this section are



4.10.D. Reduction with Formic Acid

Reduction of iminium salts proceeds by hydride transfer, with formation of carbon dioxide.⁶³² Reduction of 3-(–)-*erythro*-2-(*N*-methyl)pyrrolidiniminiumbutanoic acid (**585**) to **587** illustrates that the reaction can be stereoselective. The hydride transfer process is represented by **586**, and the stereochemistry of **587** is predicted by analysis with Cram's rule (sec. 4.7.B).⁶³³ The hydride approaches from the more sterically accessible face. A proton catalyzed tautomerization converts enamines to iminium salts, which are then reduced to the corresponding amine.⁶³⁴ Reduction of iminium salts is apparently responsible for the classical reductive methylation procedure of amines and formaldehyde in the presence of formic acid. The methylation protocol is illustrated by the *N*-methylation of the secondary amine moiety in **588** with formic acid and formaldehyde, to give a 99% yield of **589** in Tran and Kwon's synthesis of alstonerine.⁶³⁵

^{628.} Fry, J.L.; Orfanopoulos, M.; Adlington, M.G.; Dittman, Jr., W.R.; Silverman, S.B.J. Org. Chem. 1978, 43, 374.

^{629.} Boyer, J.; Corriu, R.J.P.; Perz, R.; Poirer, M.; Réyé, C. Synthesis 1981, 558.

^{630. (}a) Kaufmann, H.; Pannwitz, P. Berichte 1912, 45, 766; (b) Kovache, A. Ann. Chim. 1918, 10, 184.

^{631.} Paukstelis, J.V.; Kuehne, M.E. in *Enamines: Synthesis Structure and Reactions*, Cook, A.G. (Ed.), Marcel-Dekker, New York *1969*, pp 169-210 and 313-468.

^{632. (}a) Lukeš, R.; Jizba, J. Chem. Listy **1953**, 47, 1366 [Chem. Abstr. 49: 323g, **1955**]; (b) Idem Collect. Czech. Chem. Commun. **1954**, 19, 941, 930; (c) Leonard, N.J.; Sauers, R.R. J. Am. Chem. Soc. **1957**, 79, 6210.

^{633.} Červinka, O. Collect. Czech. Chem. Commun. 1959, 24, 1880.

^{634. (}a) Leonard, N.J.; Thomas, P.D.; Gash, V.W. J. Am. Chem. Soc. 1955, 77, 1552; (b) Bonnett, R.; Clark, V.M.; Giddey, A.; Todd, A. J. Chem. Soc. 1959, 2087.

^{635.} Tran, Y.S.; Kwon, O. Org. Lett. 2005, 7, 4289.


Several modifications of this reduction involve formates and are effective for reduction of various functional groups. A mixture of formic acid and ethyl magnesium bromide was used to reduce decanal to decanol in 70% yield.⁶³⁶ Decanal was also reduced to decanol in 69% yield by using sodium formate in *N*-methyl-2-pyrrolidinone as a solvent.⁶³⁷ Functional groups other than carbonyl derivatives can be reduced under relatively mild conditions with formate derivatives. Ammonium formate, in the presence of palladium on carbon was used to reduce an azide to a primary amine.⁶³⁸ Aliphatic nitro compounds are also converted to an amine with this reagent.⁶³⁹

4.10.E. Photoreduction

Electron transfer to certain functional groups can be induced by irradiation with light. When combined with a sensitizer and a hydrogen atom donor, reductions are possible. The basics of photochemical techniques and the use of sensitizers are discussed in Sections 11.10.B and 13.4.

In the presence of a hydrogen atom donor (usually an alcohol or an amine), carbonyl derivatives or halides can be photochemically reduced. Photolysis of ketone **590** gave the benzocyclobutane **591**,⁶⁴⁰ but photolysis in the presence of *sec*-butylamine gave alcohol **592** as the product. Photoreduction is often less stereoselective than other techniques. Both metal hydride reduction and catalytic hydrogenation of **593** gave exclusively the endo-alcohol **595**, whereas dissolving metal reduction gave 47% of the exo-isomer **594**.⁶⁴¹ Photoreduction of **593** gave a 54% yield of a 4:1 mixture of **594** and **595**.⁶⁴¹

^{636.} Babler, J.H.; Invergo, B.J. Tetrahedron Lett. 1981, 22, 621.

^{637.} Babler, J.H.; Sarussi, S.J. J. Org. Chem. 1981, 46, 3367.

^{638.} Gartiser, T.; Selve, C.; Delpeuch, J.-J. Tetrahedron Lett. 1983, 24, 1609.

^{639.} Ram, S.; Ehrenkaufer, R.E. Tetrahedron Lett. 1984, 25, 3415.

^{640.} Ito, Y.; Kawatsuki, N.; Matsuura, T. Tetrahedron Lett. 1984, 25, 2801.

^{641.} Momose, T.; Muraoka, O.; Masuda, K. Chem. Pharm. Bull. 1984, 32, 3730.



Competing photochemical pathways can be a problem when using photoreduction (sec. 13.4), including coupling, isomerization or migration of multiple bonds. Functional groups with larger quantum yields will react preferentially but this is very dependent on the wavelength of the light used for irradiation (sec. 11.10.).



Reduction of halides is a useful application of this process and there are variations that make it more useful. In a synthesis of gelsemine, Danishefsky and

co-workers showed that irradiation of bromide **596**, in the presence of the radical initiator AIBN (see sec. 13.4 and 13.3) and triphenyltin hydride led to **597** in 52% yield.⁶⁴² The reaction proceeds by formation of a carbon radical from the C-Br unit, and hydrogen transfer from the triphenyltin hydride (see sec. 13.5.D) to give **597**.

Photoreduction of imines has been used in the synthesis of various alkaloids. Irradiation of $\Delta^{1,9}$ -octa-hydroquinoline (**598**) led to a 98% yield of *trans*-octahydroquinoline (**600**). Hydrogen is transferred to the nitrogen (2-propanol is the hydrogen transfer agent), leading to the thermodynamically more stable radical (**599**).⁶⁴³ A second hydrogen transfer delivers the hydrogen to the bottom face of **599** to give **600**.



^{642.} Ng, F.W.; Lin, H.; Danishefsky, S.J. J. Am. Chem. Soc. 2002, 124, 9812.

^{643.} Hornback, J.M.; Proehl, G.S.; Starner, I.J. J. Org. Chem. 1975, 40, 1077.

4.10.F. Enzymatic Reductions

Enzymes, and biocatalysts in general, are increasingly available and important tools for the reduction of organic compounds.⁶⁴⁴ Enzymatic reductions are often straightforward and highly stereoselective. There are now many enzymatic transformations that are compatible with the use of organic solvents,⁶⁴⁵ and the alcohol dehydrogenase obtained from *Geotrichum candidum* is active in supercritical carbon dioxide.⁶⁴⁶ Prelog studied the reduction of ketones with several enzymatic systems. Reduction of ketones with *Curvularia fulcata*, for example, gave predictable stereochemical induction based on identifying Large (L) and Small (S) groups around the parts and (this method is correctioned and parts of the par

carbonyl (this method is sometimes called **Prelog's rule**).⁶⁴⁷ If the steric difference between (L) and (S) in **601** is large enough, the enzyme delivers hydrogen from the less hindered face (over S in **601**) to give **602**. Much of the initial work in this area was done with two enzymatic systems, yeast alcohol



dehydrogenase (YAD) and horse liver alcohol dehydrogenase (HLADH). This former reagent is usually obtained from yeast and is a protein with a molecular weight of ~ 80,000, containing four subunits. The exact structure of the enzyme is not always correlated with the that portion of the structure required for reduction (the active site). Such ambiguities of structure make exact mechanistic arguments difficult. An important part of the selectivity observed with these enzymes, however, is "determined by non-bonded interactions of substrate and enzyme in the hydrogen transfer transition state".⁶⁴⁷ Prelog argued that compounds capable of assuming a diamond lattice (sec. 1.5.B) gave higher selectivities.

A common and often used enzymatic reagent is baker's yeast (*Saccharomyces cerevisiae*), and it gives selective reduction of β -keto esters and β -diketones. In the Sih and co-workers synthesis of (*L*)-carnitine,⁶⁴⁸ a dependence on the size of the ester group was discovered.



Reduction of ethyl acetoacetate (**388**) with baker's yeast gave the (S)-alcohol (**603**), but reduction of ethyl β -ketovalerate (**604**) gave the (R)-alcohol (**605**).⁶⁴⁸ Sih showed the selectivity of reduction changed from (S)-

selectivity with small chain esters to (*R*)-selectivity with long chain esters.⁶⁴⁸ The break point for selectivity occurred at a chain length of four to five carbons [RC(=O)-O(CH_n)H, n = 4, 5]. Baker's yeast has been used in many synthetic applications. Hydroxyester (**603**), for example, was used in Mori's synthesis of (*S*)-(+)-sulcatol.⁶⁴⁹ Similar, and highly selective reduction

^{644.} Nakamura, K.; Yamanaka, R.; Matsuda, T.; Harada, T. Tetrahedron: Asymmetry 2003, 14, 2659.

^{645.} Carrea, G.; Riva, S. Angew. Chem. Int. Ed., 2000, 39, 2226.

^{646.} Matsuda, T.; Harada, T.; Nakamura, K. Chem. Commun. 2000, 1367.

^{647.} Prelog, V. Pure Appl. Chem. 1964, 9, 119.

^{648.} Zhou, B.; Gopalan, A.S.; Van Middlesworth, F.; Shieh, W.-R.; Sih, C.J. J. Am. Chem. Soc. 1983, 105, 5925.

^{649.} Mori, K. Tetrahedron 1981, 37, 1341.

of β-keto esters was observed with *Rhizopus arrhizus* mediated reactions.⁶⁵⁰ Carbonyl units in more complex systems can be reduced, as in the reduction of **606** to **607** (84% yield with 95:5 er) in the synthesis of paraherquamide A by Williams and co-workers.⁶⁵¹ Baker's yeast reduction was also used for the preparation of (–)-ethyl (R)-2-hydroxyl-4-phenylbutyrate, an important intermediate for the synthesis of ACE inhibitors.⁶⁵² 1,3-Diketones are usually reduced to the β-keto alcohol. Reduction of **608** with baker's yeast, for example, gave **609**, in 50% yield, and 94% ee, in a synthesis of (–)-callystatin A by Enders and co-workers.⁶⁵³ Highly enantioselective reduction of prochiral ketones was also observed when *Daucus carota* root (carrot root) was used.⁶⁵⁴ Cultured cells of *Marchantia polymorpha* have a reductase that leads to the asymmetric reduction of 2-substituted 2-butenolides to the (*R*)-butenolide.⁶⁵⁵



Problems were encountered in the reduction of aryl β -keto esters such as the furan derivative **610**,⁶⁵⁶ where baker's yeast was unable to reduce the ketone moiety. Oishi and co-workers examined other selected yeasts including *Kloeckera saturnus*, which converted **610** to a 47:53 mixture of the syn- (**611**) and anti- (**612**) diastereomers, in 47% yield and 87% ee and 53% ee respectively.⁶⁵⁶ Another yeast (*Saccharomyces delbrueckii*) gave 43% reduction with a syn/ anti ratio of 39:61, and 99% ee of **611** and 94% ee of **612**.⁶⁵⁶

- 651. Williams, R.M.; Cao, J.; Tsujishima, H.; Cox, R. J. Am. Chem. Soc. 2003, 125, 12172.
- 652. Fadnavis, N.W.; Radhika, K.R. Tetrahedron: Asymmetry 2004, 15, 3443.
- 653. Vicario, J.; Job, A.; Wolberg, M.; Müller, M.; Enders, D. Org. Lett. 2002, 4, 1023.
- 654. Yadav, J.S.; Nanda, S.; Reddy, P.T.; Rao, .B. J. Org. Chem. 2002, 67, 3900.
- 655. Shimoda, K.; Kubota, N. Tetrahedron: Asymmetry 2004, 15, 3827.
- 656. Akita, H.; Furuichi, A.; Koshiji, H.; Horikoshi, K.; Oishi, T. Tetrahedron Lett. 1982, 23, 4051.

^{650.} Salvi, N.A.; Chattopadhyay, S. Tetrahedron: Asymmetry 2004, 15, 3397.

$\begin{array}{c} Me \\ Ph \longrightarrow CO_2Me \longrightarrow \\ 0 \\ 613 \end{array}$	\mathcal{O}_{OH}^{Me} $\mathcal{O}_{OH}^{CO_2Me}$ + 614	Ph CO ₂ Me OH 615
<u>Yeast</u>	<u>% Yield</u>	<u>618 : 619</u>
Endomycopsis fibligera	72	48:52
Hansenula anomala	44	43:57
Kloeckera saturnus	44 46	40:00
Lipomvces starkevi	15	85 - 15
Pichia farinosa	40	15:85
Pichia membranaefaciens	51	53:47
Rhodotorula glutinis	46	68:32
Saccharomyces acidifaciens	14	44 : 56
Saccharomyces debrueckii	63	28:72
Saccharomyces fermentati Candida albicans	70 26	28 : 72 17 : 83

Table 4.15. Diastereoselective Reduction of 613 by Selected Yeasts.

Oishi examined the selectivity for reduction of **613** with a variety of organisms, as shown in Table 4.15.⁶⁵⁷ In all cases, the organism produced an excess of either the syn- or the antidiastereomer (**614** or **615**). The chemical yields were poor in some cases and the reduction proceed with modest to good diastereoselectivity in other cases. The enantioselectivity of the reaction was good to excellent, with 60-99% ee observed for both the *syn-* and the *anti-* diastereomers produced. In other work, Oishi and co-workers found that selected yeasts showed different diastereoselectivity and enantioselectivity when the aryl group was changed from phenyl to thiophene.^{657a} Several strains of yeast were used but the yields were poorer than the analogous reduction of **610**. Although the diastereoselectivity was similar, changes in enantioselectivity were very pronounced.

Other organisms have been used to reduce β -keto esters. Indeed, either the (*R*)- or the (*S*)alcohol can be obtained. Bernardi et al. showed that **388** was reduced to (*S*)-alcohol **603** in 96% yield, 7:93 (*R*/*S*)- with *G. candidum*.⁶⁵⁸ The reaction medium is quite important. Nakamura et al. found, for example, that reduction of ketones with this enzyme in the presence of the hydrophobic polymer AmberliteTM XAD gave the (*S*)-alcohol in high enantiomeric excess, whereas low enantioselectivity was obtained in the absence of the polymer.⁶⁵⁹ Reduction of **388** with *Aspergillus niger* gave 98% of a 75:25 mixture favoring the (*R*)-alcohol **616**.⁶⁵⁸ α -Keto esters (glyoxalates) are reduced with yeast, as illustrated by the conversion of **617** to (*S*)-alcohol **618** in 47% yield (49% ee).⁶⁶⁰ Aryl glyoxalates are usually reduced to the (*R*)alcohol.⁶⁶⁰ It has been shown that using an acetone powder of a microorganism such as *G. candidum* led to improved stereoselectivity.⁶⁶¹ Trifluoromethyl ketones are reduced with

⁽a) Furiuchi, A.; Akita, H.; Koshiji, H.; Horikoshi, K.; Oishi, T. *Chem. Pharm. Bull.* 1984, 32, 1619; (b) Akita, H.; Furuichi, A.; Koshiji, H.; Horikoshi, K.; Oishi, T. *Ibid.* 1984, 32, 1342; (c) *Idem Ibid.* 1983, 31, 4376.

^{658.} Bernardi, R.; Cardillo, R.; Ghiringhelli, D. J. Chem. Soc. Chem. Commun. 1984, 460.

^{659.} Nakamura, K.; Fujii, M.; Ida, Y. J. Chem. Soc. Perkin Trans. 1 2000, 3205.

^{660.} Iriuchijima, S.; Ogawa, M. Synthesis 1982, 41.

^{661.} Matsuda, T.; Harada, T.; Nakajima, N.; Nakamura, K. Tetrahedron Lett. 2000, 41, 4135.

opposite stereochemistry relative to methyl ketones with this organism.⁶⁶² Bioreduction using methanol as a co-solvent and the fungus *Curvularia lunata* CECT 2130 gave chemoselective reduction of aromatic β -keto nitriles to the corresponding (*S*)- β -hydroxy nitriles with high enantioselectivity.⁶⁶³



Isolated ketone units can also be reduced with baker's yeast.⁶⁶⁴ In a synthetic example, ketone moiety of the piperidone unit in **619** was reduced with baker's yeast to give a 40% yield of **620** (98% ee) in Takeuchi's synthesis of isofebrifugine.⁶⁶⁵



Veschambre used *Beauveria sulfurescens* for the reduction of conjugated carbonyls. *trans*-Crotonaldehyde was reduced to but-(2E)-en-1-ol in 80% yield.⁶⁶⁶ 2-Methyl-2-pentenal (**621**), however, gave a mixture of 31% of the conjugated alcohol (**622**) and 69% of the completely reduced alcohol (2-methyl-1-pentanol, **623**).⁶⁶⁶ Later work showed this microbial reduction gave the (*S*)-alcohol by a stepwise process in which the conjugated double bond was reduced first, establishing the (*S*)-stereochemistry, followed by reduction of the aldehyde moiety to the alcohol.^{666b} Veschambre established a rule for this reduction, **Veschambre's rule**. The hydrogen is delivered to the double bond α to the carbonyl from the front or back depending on the relative bulk of R¹ and R², which is simply a modification of Prelog's Rule. Reduction of geranial with baker's yeast gave (*R*)-citronellol, consistent with the prediction. The (*Z*)-isomer neral was predicted to give the (*S*)-isomer, but reduction with baker's yeast gave a 6:4 (*R*/*S*) mixture, possibly due to isomerization of the double bond in neral prior to delivery of hydrogen.^{666b} Shimoda and co-workers found that *Synechococcus sp.* PCC 7942, a cyanobacterium, reduced both the endocyclic double bond and s-*trans*-enones as well as the exocyclic double bond of

^{662.} Matsuda, T.; Harada, T.; Nakajima, N.; Itoh, T.; Nakamura, K. J. Org. Chem. 2000, 65, 157.

^{663.} Dehli, J.R.; Gotor, V. Tetrahedron: Asymmetry 2000, 11, 3693.

^{664.} Lieser, J.K. Synth. Commun. 1983, 13, 765.

^{665.} Takeuchi, Y.; Azuma, K.; Takakura, K.; Abe, H.; Harayama, T. Chem. Commun. 2000, 1643.

^{666. (}a) Desrut, M.; Kergomard, A.; Renard, M.F.; Veschambre, H. *Tetrahedron* **1981**, *37*, 3825; (b) Bostmembrun-Desrut, M.; Dauphin, G.; Kergomard, A.; Renard, M.F.; Veschambre, H. *Ibid.* **1985**, *41*, 3679.

s-cis-enones with high enantioselectivity.667

Another common organism for reduction of the carbonyl group is Thermoanaerobium brockii (238), first mentioned in Section 4.7.A, in Table 4.5. Keinan et al. showed that small ketones such as 2-butanone were reduced by T. brockii to give (R)-2-butanol, in 12% yield and 48% ee, but longer chain ketones such as 2-nonanone were reduced to the (S)-alcohol [624, 85% yield and 96% ee].²⁶⁶ An alcohol dehydrogenase found in *Thermoanaerobacter ethanolicus* reduces ethynyl ketoses such as 625 to 626 in good yield, and high enantioselectivity [in this case 626 was isolated in 50% yield and >98% ee, (S)].⁶⁶⁸ These examples illustrate typical enantioselectivity of the reduction and that the selectivity depends on the size and nature of the groups around the carbonyl. Changes in selectivity are explained by knowledge of the active site of the enzyme. The carbonyl is bound close to a nicotinamide moiety in the coenzyme. Two alkyl sites are also present with the smaller alkyl group lying closer to the nicotinamide having the greater affinity.²⁶⁶ Keinan and Lamed²⁶⁶ suggested the small alkyl site can accommodate groups smaller than *n*-propyl. For methyl-alkyl ketones, if the alkyl is methyl, ethyl, isopropyl or cyclopropyl, the (R)-alcohol predominates but if the alcohol group is larger than *n*-propyl the (S)-alcohol predominates. For internal ketones (alkyl-alkyl) the (S)-alcohol is usually the major product.⁶⁶⁹ It appears that various yeast preparations and T. *brockii* are the most commonly used reducing organisms. New organisms are being used on a regular basis. Lyophilized cells from Rhodococcus ruber DSM 44541 for example, reduced ketones to alcohols in good yield, and with excellent enantioselectivity.⁶⁷⁰ The low cost and high selectivity of such enzymatic and microbial reagents foretell an increasingly important role in organic synthesis.



4.11. CONCLUSION

It is obvious from this chapter that reductive processes are important in organic synthesis. The diastereoselectivity and enantioselectivity of many reducing agents are important for fixing stereogenic. An attempt has been made to show how reagents were developed as well as their

^{667.} Shimoda, K.; Kubota, N.; Hamada, H.; Kaji, M.; Hirata, T. Tetrahedron: Asymmetry 2004, 15, 1677.

^{668.} Heiss, C.; Phillips, R.S. J. Chem. Soc. Perkin Trans. 1 2000, 2821.

^{669.} Seebach, D.; Züger, M.F.; Giovannini, F.; Sonnleitner, B.; Friechter, A. Angew. Chem. Int. Ed. 1984, 23, 151.

^{670.} Stampfer, W.; Kosjek, B.; Faber, K.; Kroutil, W. J. Org. Chem. 2003, 68, 402.

chemoselectivity.

Chapter 5 will introduce reactions associated with hydroboration. This important synthetic methodology is a logical extension of the borohydride and borane reductions seen in this chapter. Chronologically, the reductive capabilities of boranes preceded the alkene addition reaction, which is the heart of hydroboration. In part, this is why hydroboration is presented after reduction.

It is also noted that the stereochemical models introduced in this chapter will be used continuously in succeeding chapters. Addition of Grignard reagents and other organometallics to carbonyls generally follow Cram's rule or the Felkin-Anh model. Chelation control will be important in many reactions including enolate alkylation reactions. This chapter has therefore been a vehicle for introducing not only reduction but the stereochemical basis for all of organic chemistry.

HOMEWORK

1. Predict the correct diastereomeric product using (a) the appropriate Cram model and (b) the Felkin-Anh model. In each case, draw the model for that specific reaction.



2. Predict the major product and explain the stereochemistry for that product.



3. In each case, predict the major diastereomer. Explain your answer.





4. Explain why there is such a difference in selectivity for reduction of this conjugated ketone when the reducing agent is changed.



5. Briefly discuss this transformation.



6. Predict the major product of both reactions, (A and B), predict the stereochemistry of each product, and explain your choices.



7. Briefly discuss the following transformation, particularly focusing attention on the stereochemistry.



8. Explain each of the following observations or products.



- (c) Treatment of benzene with Na/NH₃/EtOH gives 1,4-cyclohexadiene, whereas similar treatment of cyclohexene with this reagent gives no reaction.
- (d) Birch reduction of anisole leads to 1-methoxy-1,4-cyclohexadiene but reduction of benzoic acid give 3-carbalkoxy-1,4-cyclohexadiene.

 $\bar{C}O_2Et$

OSiMe2t-Bu

- (e) Reduction with LiAlH₄ gives a diol but reduction with diborane gives a hydroxy ester.
- (f) Diimide reduces unconjugated alkenes faster than conjugated alkenes.
- (g) Reduction of A and B with zinc borohydride leads to opposite stereochemical results. A





9. For each transformation, give two <u>different</u> reagents that will successfully complete the given conversion.

$$n-C_5H_{11}$$
 C_1 $n-C_5H_{11}$ H $n-C_5H_{11}$ O_{OTs} $n-C_5H_{11}$ CH_3

10. In each case, predict the major product of the reaction shown.







11. In each case, provide a suitable synthesis showing all intermediate products and all reagents.





12. Show a complete synthesis for each of the following. Use any starting material of your choosing, that contains six carbons or less, but you must find it in a current catalog from a chemical company (give the source and price of your starting material). Show a retrosynthetic analysis and synthesis for each molecule.



13. Give reagents that will accomplish each of the following selective transformations.





Hydroboration

INTRODUCTION 5.1.

chapter

In chapter 4, borane and alkylborane reagents were introduced as powerful and selective reducing agents. The Lewis acidity of borane (BH_3) led to interesting differences in reducing power when compared to $LiAlH_4$ and $NaBH_4$ derivatives. An example of this difference was Brown and co-worker's discovery that diborane (B_2H_6) reacted with alkenes in ether solvents

5

 6^{R} + $B_{2}H_{6}$ $2\binom{R}{1}_{3}B_{3}$ to form trialkylboranes (1).¹ Brown's monograph described formation of an alkylborane from an alkene using NaBH₄/AlCl₃, NaBH₄/BF₃ or diborane itself.²

Continuing interest in this reaction led to development of a large number of functional group transformations and carbon-carbon bond-forming reactions that utilized mono-, di-, trialkyl, and alkenylboranes. This work was cited in the Nobel Prize for Chemistry awarded to H.C. Brown in 1979. Hydroboration is included in organic synthesis because the technique makes several unique transformations possible, and they are detailed in this chapter. A discussion of hydroboration following the discussion of the reducing properties of boranes (in Chap. 4) is both historically correct and conceptually useful. Where appropriate, the diastereoselectivity and the enantioselectivity of hydroboration reactions will be discussed. In addition to the functional group transformations that are available via hydroboration, the reactions presented in this chapter are a useful review of many reaction types encountered in earlier chapters.

5.2. PREPARATION OF ALKYL AND ALKENYL BORANES

Alkyl Boranes 5.2.A.

Diborane reacts with alkenes in ether solvents to form alkylboranes. This important finding apparently resulted from an observation by Brown that reduction of ethyl oleate in ether solvents and in the presence of a Lewis acid, consumed 2.4-2.5 hydrides per equivalents and three equivalents when a larger excess of the reagent was used.³ Brown discovered that borane had

^{1. (}a) Brown, H.C.; Subba Rao, B.C. J. Am. Chem. Soc. 1956, 78, 5694; (b) Idem J. Org. Chem. 1957, 22, 1136.

^{2.} Brown, H.C. Hydroboration, W.A. Benjamin, New York, 1962.

^{3.} Reference 2, p 42.

added to the π bond of the alkene moiety generating a monoalkylborane (2), and this is a general reaction. If a sufficient quantity of alkene is present, one of the hydrogen atoms on boron (see 2) can react with a second equivalent of alkene to give the dialkylborane (3) and with a third equivalent to give the trialkylborane (1).² The reaction of diborane with unsaturated molecules had been reported earlier by Stock and Kuss,⁴ in the explosive reaction of acetylene and diborane at 100°C. In 1948, Hurd reported that alkenes reacted with diborane at elevated temperatures to form a trialkylborane,⁵ but the reaction was slow at 100°C (24 h) and even slower at ambient temperatures. This earlier work with borane did not use an ether solvent, but Brown's work showed that ethers had a catalytic effect on the addition of borane to alkenes. Although the "reaction of diborane with pure olefins is indeed quite slow, addition of mere traces of ether changed the initially slow reaction to a fast one."⁶ This rate acceleration allowed alkylboranes to be readily formed^{1a,7} under relatively mild conditions, allowing them to be used in synthesis.

$$\xrightarrow{R} \xrightarrow{BH_3} H \xrightarrow{H} \xrightarrow{H} \xrightarrow{R} \xrightarrow{R} H \xrightarrow{R}$$

An excellent *in situ* preparation of diborane results from the reaction of boron trichloride (BCl₃) or boron trifluoride (BF₃) with sodium borohydride in the presence of alkenes, as mentioned above. This reagent gave virtually instantaneous conversion of an alkene to a trialkylborane at ambient temperatures, when done in a ether solvent.⁸ When diborane was isolated and purified it also reacted with alkenes, rapidly and quantitatively in ether solvents. Homoallylic phosphine boranes undergo intramolecular hydroboration, in the presence of triflic acid.⁹

5.2.A.i. General Properties of Borane Addition to Alkenes. When borane reacts with alkenes, there are several predictable characteristics.¹⁰

1. Borane reacts with alkenes and alkynes rapidly and quantitatively (in most cases) by addition of H and B to the π - bond of an alkene or an alkyne, to give an alkylborane or an alkenylborane, respectively.^{2,11}

$$R \xrightarrow{R} \xrightarrow{BH_3} \begin{pmatrix} H & R \\ H & & \\ H & & \\ & & 3 \end{pmatrix}_B \qquad R \xrightarrow{BH_3} \begin{pmatrix} R & R \\ H & & \\ & & \\ & & & & \\ & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & &$$

- 4. Stock, A.; Kuss, E. Berichte 1923, 56, 789.
- 5. Hurd, D.T. J. Am. Chem. Soc. 1948, 70, 2053.
- 6. Reference 2, p 44.
- 7. Brown, H.C.; Subba Rao, B.C. J. Am. Chem. Soc. 1959, 81, 6423.
- 8. Brown, H.C.; Subba Rao, B.C. J. Am. Chem. Soc. 1959, 81, 6428.
- 9. Shapland, P.; Vedejs, E. J. Org. Chem. 2004, 69, 4094.
- 10. Brown, H.C. Pure Appl. Chem. 1976, 47, 49.
- 11. (a)Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, New York, **1972**; (b)Brown, H.C.; Kramer, G.W.; Levy, A.B.; Midland, M.M. *Organic Synthesis Via Boranes*, Wiley Interscience, New York, **1975**.

2. The reaction proceeds by cis addition of H and B, probably via a four-center transition state such as **4**.



3. The boron adds regioselectively at the less sterically hindered position, as shown in the reaction with 2-methyl-1-butene.



4. The boron adds stereoselectively to the less sterically hindered face of the alkene. Reaction with norbornene, for example, gave 99.6% of the exo-borane (5) with only 20.4% of the endo- borane.¹² This is consistent with the normal addition of reagents to the exo face of norbornyl derivatives (sec. 1.5.E).



5. Hydroboration proceeds without skeletal rearrangement, at normal temperatures, as in the hydroboration of α -pinene (6) to give 7.^{2,11}



- 6. In ether solvents, a wide range of other functional groups can be tolerated, even reducible ones such as esters, if the stoichiometry of the reagent is controlled.
- 7. The organoborane product can be oxidized, eliminated, rearranged, protonated and aminated, leading to a large number of functional group transformations.

As noted in (3), borane adds selectively to the less sterically hindered carbon of the alkene or alkyne, but *mixtures* of Markovnikov product (addition of boron to the most hindered carbon) and anti-Markovnikov (addition of boron to the less hindered carbon) product are usually observed. This selectivity is best under-stood by examining the four-center transition state required for the addition (see 4). When borane approaches the alkene unit of 2-methylpropene, two orientations are possible (8 and 9). In 8, the BH₂ moiety is positioned over the less hindered

^{12.} Brown, H.C. Chemistry in Britain 1971, 7, 458.

carbon bearing the hydrogen atoms $[BH_2 \leftrightarrow H_2C=]$ because this minimizes the destabilizing steric interactions with the methyl groups on the alkene $[BH_2 \leftrightarrow Me_2C=]$ found in the other orientation (9). In other words, this interaction destabilizes 9 and leads to selective delivery of boron to the less hindered carbon via 8.



In the reaction of monosubstituted alkenes with diborane, the steric interaction between the BH₂ mojety of the borane and the single alkyl group on the π bond is sufficient to give >90% selectivity for the anti-Markovnikov product 10, over 11 (93:7 for $R^1 = Et$, R^2 , $R^3 = H$).¹³ With di- and trisubstituted alkenes the increased steric interaction between the boron and alkyl groups on the alkene led to extremely high selectivities ($R^1 = Ph$ and $R^2 = Et$ in 10, for example). Electronic effects are also a factor in the reaction of styrene, which gave only 80% selectivity for 10. This electronic effect diminishes with distance (as when R^1 is benzyl, which behaves as if it were a simple alkyl group). When there is little steric difference between two groups in disubstituted alkenes (the B–H \leftrightarrow R¹ and B–H \leftrightarrow R³ interactions are about the same, as when R¹ = Et and R^3 = Me), poor selectivity was observed, giving close to a 1:1 mixture of 10 and 11. cis Alkenes with large groups attached to the π -bond generally gave good selectivity for the anti-Markovnikov borane, but cis alkenes with small groups showed poor selectivity. In trans alkenes, large differences in the size of substituents were less important, although there was some selectivity for addition of boron to the carbon bearing the smaller substituent. Addition of boron occurred preferentially at the monosubstituted carbon in trisubstituted alkenes. In a synthesis of the bis(spiroacetal) moiety of spirolide B by Brimble and Meilert,¹⁴ for example, the dimethyl sulfide complex of borane reacted with 12 to give a 78% yield of primary alcohol 13 after treatment of the initially formed alkylborane with sodium hydroxide and hydrogen peroxide (see sec. 5.4.A).



There are three B-H bonds in borane and therefore three equivalents of hydride are available

13. Reference 2, pp 113-122.

14. Meilert, K.; Brimble, M.A. Org. Lett. 2005, 7, 3497.

to react with three equivalents of alkene, which would give a trialkylborane. The boronalkyl interactions in the four-center transition state (8 or 9) largely control the reaction, but destabilizing steric interactions between alkyl substituents attached to the boron in the alkylborane products are also important. Terminal alkenes (such as 1-decene) and relatively unsubstituted alkenes (such as 2-butene or cyclohexene) usually react with borane to give trialkylboranes (R₃B).¹⁵ Relatively unhindered trisubstituted alkenes such as 2-methyl-2-butene usually give a dialkylborane (R₂BH),¹⁵ and hindered alkenes such as *tert*-butylcyclohexene or 2,4,4-trimethyl-2-butene lead to a monoalkylborane (RBH₂).¹⁵ As the steric bulk of the alkyl substituent on the π bond increases, the rate of addition of the initially formed organoborane product to unreacted alkene decreases.

Borane can react with an alkene to give a monoalkylborane. The reactive unit of borane is B–H, and a monoalkylborane has two B–H unit available. It is therefore reasonable that a monoalkylborane can also react with an alkene, forming a dialkylborane. Since the dialkylborane has one B–H unit, it can react with an alkene to form a trialkylborane. Monoalkyl and dialkylboranes are less reactive than diborane itself in reactions with alkenes because alkyl groups are electron releasing, diminishing the Lewis acidity of the boron. The mono-alkylborane derived from 1,2-dimethylcyclopentene, for example, does not react with additional 1,2-dimethylcyclopentene but it reacts rapidly with a less hindered alkene such as 1-butene to give a mixed alkyl trisubstituted borane. Similarly, disubstituted boranes react with 1 equivalent of a new alkene to give a mixed trialkylborane, but they are less reactive than monoalkylboranes. The point of these observations is that mono- and dialkylboranes function as new hydroboration reagents, reacting with alkenes in a manner analogous to borane. no hydrogen remains on boron If a trialkylborane is formed, and it cannot react with additional alkene. Brown used this premise to generate several important organoboranes¹⁶ that have

become commercially available. Reaction of 2-methyl-2-butene gives 14, diisoamylborane (diisoamylborane = disiamylborane = Sia₂BH), 2,3-dimethyl-2-butene gives 15 (*tertiary* hexylborane = thexylborane, ThexBH₂)





and α -pinene (6) gives 16 (diisopinocampheylborane = Ipc₂BH). Dienes form cyclic boranes, as with the reaction of reaction of 2,4-dimethyl-1,4-pentadiene (17) to give 18 (3,5-dimethylborinane). A highly useful

borane reagent is prepared by the reaction of 1,5-cyclooctadiene (19) and borane, giving 20 (9-borabicyclo-[3.3.1]nonane = 9-BBN).

^{15.} Reference 2, pp 102-112.

^{16.} Lane, C.F. Aldrichimica Acta 1973, 6, 21.



5.2.A.ii. Regioselectivity and Diastereoselectivity. There are two stereochemical advantages in using hindered alkylboranes as hydroboration reagents: increased anti-Markovnikov selectivity and enhanced cis selectivity. This selectivity can be seen in Table 5.1,¹⁷ which compares reactions of borane, disiamylborane and 9-BBN with several alkenes. Hindered boranes show greater selectivity for delivery of boron to the less sterically hindered carbon of terminal alkenes (to =CH₂) than does diborane. Perhaps the most dramatic increase in selectivity is observed with internal alkenes since they show poor selectivity with borane, whereas the hindered 9-BBN delivers hydrogen selectively to the less hindered carbon in such systems. Borane gave only 80% addition to the terminal carbon of styrene upon reaction, despite the electronic effects of the phenyl. When the bulky 9-BBN added to styrene, however, >98.5% addition to the terminal carbon was observed. It is clear from Table 5.1 that 9-BBN and disiamylborane react with alkenes to give extremely high yields of the anti-Markovnikov addition product. These reagents are more expensive, but 9-BBN is more stable than the pyrophoric diborane, which is almost always used in solution or generated *in situ*.

^{17. (}a) Cragg, G.M.L. Organoboranes in Organic Synthesi, Marcel-Dekker, New York, 1973, pp 63-84; (b) Brown, H.C. Aldrichimica Acta 1974, 7, 43.

Alkene ^a	BH ₃		Sia ₂ BH		9-BBN	
	<u>a</u>	<u>b</u>	<u>a</u>	<u>b</u>	<u>a</u>	<u>b</u>
	45	45	57	33		
	56	43	87	3	90	3
	51	39	86	5		
\sum_{a}^{b}			98	2	94	1
	94	06	99	1	99.9	0.1
cl b = a	60	40	98	2		
	57	43	97	3	99.9	0.1
b = a	81	19	98.5	1.5		
	48	40	60	40		
^a Ca is always the less sterically hindered carbon. For disubstituted alkenes, Ca is the carbon distal (most distant from) a pedant substituent. a and b refer to the points of attachment of the boron atom.						

 Table 5.1.
 Enhanced Anti-Markovnikov Selectivity with Bulky Boranes



Diborane as well as mono- and dialkylboranes give cis addition in reactions with alkenes, as noted above, which is a result of the four-center transition state in which the boron and hydrogen are delivered from the same face, as illustrated by hydroboration of 1-methylcyclopentene with

 R_2BH to give 21. The methyl-bearing sp² carbon of methylcyclopentene is a prochiral center, and addition of the borane will generate the (*R*) and (*S*) enantiomers of the trans-isomer. Hydroboration produces only the *trans*-borane (21) via cis-addition of BR_2 and H (see 2 in sec. 5.2.A.), making the addition highly diastereoselective. When the compound contains a substituent, diastereoselectivity is determined by approach of the borane from the less sterically hindered face of the alkene (secs. 5.2.A.ii, 5.4.B). In general, boranes containing bulky substituents give greater selectivity. Similar factors were discussed for hydride reductions (sec.

4.7.B). For cyclic molecules^{18,17} possessing an exocyclic methylene group, attachment of boron occurs almost exclusively at the terminal alkene carbon. As seen for the reaction of **22** and **23** with diborane (the values in parentheses



are percentage yields of each organoborane product obtained by reaction from that face), the preferred face of attack is path b (with the major product resulting from attack at the terminal carbon of the alkene). The borane is sufficiently bulky that the diaxial interaction of the axial

^{18.} Klein, J.; Lichtenberg, D. J. Org. Chem. 1970, 35, 2654

hydrogens at C3 and C5 inhibits path a (opposite the effect seen with hydride reduction of cyclohexanone derivatives, sec. 4.7.C, where path a is preferred). As the size of the borane increases, the selectivity for path b will also increase.

When the alkene is internal and unsymmetrical, as in 3-methyl-1-cyclohexene (24), the reaction is more complicated. In addition to the two faces (top and bottom) of the molecule, there are two different and reactive sp² carbons of the alkene. Hydroboration leads to four products 25-28, although diborane gives little regioselectivity (32:34 for top attack to give 25 and 26, and selectivity of only 18:15 for bottom attack to give 27 and 28). There is a preference for delivery of the boron to the face opposite the methyl group (32:18 and 34:15), making 25 and 26 the major products.¹⁷ Similar results were observed when 1,6-dimethyl-cyclohexene reacted with borane.¹⁹



Reactions of borane with bicyclic alkenes give products with stereochemistry similar to that observed for reduction of bicyclic ketones with hydride reducing agents. Boranes add to norbornene derivatives from the exo face (**29** gave 85% exo attack upon reaction with diborane). In **29-32**, all values are percentage yields of the organoborane products obtained by reaction from that face. Interestingly, only 80% exo attack was observed when **29** reacted with disiamylborane,¹⁷ and the size of the borane appears to have little effect on selectivity. Substituents at the 7-position block the exo face and reaction of **30** with diborane gave 56% of the endo product, with only 10% of the exo product. In this case, reaction of **30** and disiamylborane gave 85% of the endo product, showing enhanced selectivity.¹⁷ Similar results were observed when the C=C unit is within the ring.²⁰ Reaction of 2-methylbicyclo[2.2.1]hept-2-ene (**31**) with diborane shows the expected exo selectivity and also a preference for attack at the less hindered carbon. The C=C unit in **32** has no steric features to distinguish one carbon from the other, and reaction with diborane gives essentially a 1:1 mixture of regioisomers, although there is a marked preference for exo delivery of boron.



^{19.} Pasto, D.J.; Klein, F.M. J. Org. Chem. 1968, 33, 1468.

20. Brown, H.C.; Kawakami, J.H. J. Am. Chem. Soc. 1970, 92 1990.

When the alkene is part of an edge fused bicyclic system, regio- and stereoselectivity may be influenced by the conformation of the molecule and the relative stereochemistry of the substituents. Hydroboration of **33**, in Heathcock and Kelly's synthesis of eudesmanes, 21,17 led to a 66:34 mixture of boranes with attack from the top face predominating (giving **34**).



MOLECULAR MODELING: Stereochemistry in Hydroboration

Looking at an accurate 3D model of reactants (as opposed to a 2D sketch) is often sufficient to identify the likely product of a reaction. For example, a model for the tricyclodecene derivative (top left) shows distinct "convex" (*exo*) and "concave" (*endo*) faces. This means that there are two different ways for the reagent to approach the carbon-carbon double bond. The model shows that the *exo* face is less crowded, suggesting that hydroboration will occur preferentially here and give the stereochemistry for the alcohol shown in the drawing. This "conclusion" can be amplified by changing to a space-filling model, which reveals the actual size and shape of a molecule.



Of course, "crowded" refers to reactants. While the *Hammond Postulate* tells us that the transition state will resemble the reactants if the process is sufficiently *exothermic*, don't forget this is just a postulate. Transition state calculations based on quantum chemical methods are the "gold standard" for modeling selectivity. For the reaction described above, they show that the transition state for hydroboration onto the convex face (top center) is 45 kJ/mol lower in energy than that for reaction onto the concave face (top right). This difference is large enough that only one product will be seen.

Transition state models are not only able to identify the favored direction for approach of a reagent, but are also able to account for changes in selectivity (differences in transition-state energies leading to different products) with change in reactants. For example, calculations show that replacing the methyl ester by hydrogen lowers the difference between the *exo* and *endo* transition states to 25 kJ/mol (*exo* is still favored). Compare the *exo* (bottom center) and *endo* (bottom left) transition states with those of the methyl ester. Has the cavity opened up in response to removal of the ester group?

Although hindered alkylboranes are relatively stable, dialkylboranes can disproportionate, which limits their utility in reactions with alkenes. One solution to this problem was the discovery that boranes containing heteroatoms stabilize the borane and are easy to prepare. Diborane reacts with alcohols such as methanol to form dimethoxyborane [(MeO)₂BH].²²

^{21.} Heathcock, C.H.; Kelly, T.R. Tetrahedron 1968, 24, 1801.

^{22.} Brown, H.C.; Bigley, D.B. in Reference 11b, p 44

2 MeOH
$$\xrightarrow{BH_3, THF}$$
 (MeO)₂B-H + 2 H₂

Similarly, alkyl glycols react to give cyclic dialkoxyborates²³ but these are somewhat unreactive in subsequent reactions with alkenes. Catecholborane (36, formed by the reaction of borane with catechol, **35**) reacts with alkenes to give an alkoxyborinate,²⁴ but the hydroboration reaction requires heating to $\sim 100^{\circ}$ C. An example is the reaction of **36** with norbornene to form the exo-alkoxyborinate (37).²⁴ An advantage in using catecholboranes is that the boronic acid byproducts are more easily hydrolyzed than the corresponding dialkylboranes (sec. 5.4.A). A synthetic example is taken from a synthesis of apoptolidinone by Crimmins and co-workers,²⁵ where **38** reacted with **36** and Wilkinson's catalyst $[ClRh(PPh_3)_3]^{26}$ with high selectivity for the primary position, and oxidation gave 39 in excellent yield. Note that the monosubstituted alkene reacted preferentially to the trisubstituted alkene in 38.



Chloroboranes are another class of heteroatom-substituted boranes. Dichloroborane (Cl₂BH) and monochloroborane (ClBH₂) are formed by the reaction of diborane with varying proportions of boron trichloride etherate (BCl₃•OEt₂). In ether solvents, both boranes are formed as their etherate complex.²⁷ An alternative synthesis reacted HCl with borane•THF,²⁸ but reduction of boron trichloride with lithium borohydride in ether proved to be the most useful route.²⁷

 $\begin{array}{c} \begin{array}{c} H_2B\text{-}Cl\text{-}OEt_2 \\ \hline \\ ether, 0^\circ\text{C}, 1 \text{ h} \end{array} \begin{pmatrix} & & & \\ & &$

regioselectivity for attachment of boron at the terminal carbon of 1-alkenes (anti-Markovnikov addition).³⁰ 1-Hexene gave 99.5% of the terminal borane, for example, whereas similar reaction with diborane gave only 94%.^{17b} Similarly, styrene reacted to give 96% of the terminal borane

- 23. Woods, W.G.; Strong, P.L. J. Am. Chem. Soc. 1966, 88, 4667.
- 24. Brown, H.C.; Gupta, S.K. J. Am. Chem. Soc. 1971, 93, 1816.
- 25. Crimmins, M.T.; Christie, H.S.; Chaudhary, K.; Long, A. J. Am. Chem. Soc. 2005, 127, 13810.
- 26. Used to catalyze the hydroboration reaction. See Evans, D.A.; Fu, G.C.; Hoveyda, A.H. J. Am. Chem. Soc. 1992. 114. 6671.
- 27. Brown, H.C.; Tierney, P.A. J. Inorg. Nucl. Chem. 1959, 9, 51.
- 28. Zweifel, G. J. Organomet. Chem. 1967, 9, 215.
- 29. Brown, H.C.; Ravindran, N. J. Am. Chem. Soc. 1972, 94, 2112.
- 30. Brown, H.C.; Ravindran, N. J. Org. Chem. 1973, 38, 182.

compared with 81% from diborane despite the electronic effects of the phenyl group. Internal alkenes show less selectivity as in the reaction of 4-methyl-2-pentene, which gave only 60% delivery of boron to the 2-position. 2,3-Dimethyl-2-butene, however, reacted to give 99.7% of product with the boron moiety at the 2-position. The addition of chloroborane to alkenes is less influenced by steric factors than the similar addition of mono- or dialkylboranes, accounting for the generally poorer selectivity exhibited by chloroborane in its reactions with internal alkenes.

5.2.A.iii. Isomerization of Alkylboranes. One of the early discoveries of organoboranes was their tendency to undergo isomerization if the temperature approached 160°C. This isomerization involves migration of the boron from a more to a less substituted position, usually giving the terminal alkylborane as the predominant isomer.³¹ Reaction of 3-hexene with borane initially gave 3-hexylborane **45**, but heating induced rearrangement to 1-hexylborane (**46**). This isomerization can be used to advantage in subsequent reactions of boranes, such as oxidation to alcohols (sec. 5.4.A). If the initial hydroboration occurs *on* a ring (as in **47** from the cyclic alkene), isomerization will put boron at the terminal position of an alkyl side chain, as in the conversion of 1-methylcyclohexene to **49** via heating **47** to form **48**, followed by subsequent heating with 1-decene to give tridecylborane and **49**.^{32,33b}



A sacrificial alkene such as 1-decene or 1-hexadecene can be added to drive the overall reaction toward a specific target alkene. Mechanistically, thermal isomerization apparently involves a series of reversible elimination reactions of borane followed by readdition in an anti-Markovnikov manner.² If the sacrificial alkene has a significantly higher boiling point, the desired alkene can be distilled from the reaction medium.^{31a} The sacrificial alkene must not boil < 160°C, however, which is the temperature required for borane isomerization. This protocol makes it possible to isomerize the double bond of an alkene to a less substituted isomer, a process that Brown termed **contrathermodynamic isomerization**.^{33,34} Similar to the preparation of **49**, α -pinene was converted to β -pinene in 54% yield³² by contrathermodynamic

^{31. (}a) Brown, H.C.; Subba Rao, B.C. J. Am. Chem. Soc. 1959, 81, 6428; (b) Brown, H.C.; Zweifel, G. Ibid. 1966, 88, 1433.

^{32.} Brown, H.C.; Zweifel, G. J. Am. Chem. Soc. 1967, 89, 561.

 ⁽a) Brown, H.C.; Bhatt, M.V. J. Am. Chem. Soc. 1966, 88, 1440; (b) Brown, H.C.; Bhatt, M.V.; Munekata, T.; Zweifel, G. Ibid. 1967, 89, 567.

^{34.} Brown, H.C., Subba Rao, B.C. J. Org. Chem. 1957, 22, 1137.

isomerization. Significant amounts of endocyclic isomers often accompany this hydroborationbond migration process with exocyclic alkenes, and separation of these isomeric by-products can be difficult, limiting the utility of this process.

5.2.A.iv. Hydroboration of Dienes and Heteroatom-Containing Alkenes. Hydroboration has also been reported with a variety of heteroaryl alkenes.³⁵ The regioselectivity of hydroboration with 2-vinylpyridine, 3-vinylpyridine, 4-vinylpyridine, as well as 2-vinylfuran, 2-(2-propenyl) furan, 2-vinylthio-phene, 2-(2-propenyl)thiophene were compared with styrene, which showed the expected selectivity for addition of boron to the terminal carbon. In general, the presence of nitrogen in the pyridyl derivatives changed the selectivity for addition from the terminal carbon (the β -carbon) to the α -carbon, even when the reagent was not sterically hindered. Nitrogen releases electrons to the π -bond and the carbon closest to nitrogen receives the most electron density. In reactions with diborane, this electronic effect made attack at C_a preferred when the nitrogen was ortho (2-pyridyl) or para (4-pyridyl). The meta compound (3-pyridyl) does not transmit electrons through the π -system as effectively, and the selectivity was poorer. When excess borane was used, the first equivalent coordinated to nitrogen and the second to the alkene. Addition of BF₃ had the same effect, allowing the subsequent addition of a single equivalent of borane. The bulky reagent 9-BBN showed high selectivity for attack at C_b with 2-pyridyl and 3-pyridyl substituted alkenes, but the electronic effect of the aromatic groups also led to significant amounts of attack at Ca. When the nitrogen was further away (as in 4-pyridyl), the steric and electronic effects are less important and attack at C_a is preferred. Analogous effects were observed with the furan and thiophene derivatives.

Hydroboration of conjugated dienes raises the usual issue, 1,2- versus 1,4-addition. Conjugated dienes such as 1,3-cyclohexadiene (**50**) gave mainly 1,4-addition (85:10 **51**:**52** with 9-BBN is a typical example). Reaction with dibromoboranes, however, favors the dihydroboration product.³⁶ In the case of the symmetrical dienes **51** and **52** could result from 1,2-addition to different carbons of one C=C moiety. In this example, however, **51** is considered to be a 1,4-addition product and **52** is considered to be a 1,2-addition product. As the size of the ring increases, dihydroboration increases at the expense of mono-hydroboration. Six-membered rings are less reactive in hydroboration reactions relative to larger and smaller rings.³⁷ Nonconjugated dienes such as 1,4-cyclohexadiene show the expected independence of the double bonds, giving a mixture of mono-hydroboration and dihydroboration products.³⁷



 ⁽a) Brown, H.C.; Vara Prasad, J.V.N.; Zee, S.-H. J. Org. Chem. 1986, 51, 439; (b) Brown, H.C.; Vara Prasad, J.V.N.; Gupta, A.-K. Ibid. 1986, 51, 4296.

^{36.} Brown, H.C.; Bhat, K.S. J. Org. Chem. 1986, 51, 445.

^{37.} Zweifel, G.; Nagase, K.; Brown, H.C. J. Am. Chem. Soc. 1962, 84, 190.

5.2.B. Alkenylboranes



Boranes add to one π bond of an alkyne just as they add to the π bond of an alkene and the product is the corresponding alkenyl (vinyl) borane, which undergoes many of the same reactions as alkylboranes.³⁸ Internal

alkynes such as 3-hexyne react with diborane to give the trialkenylborane (**53**) in moderate yield, but terminal alkynes such as 1-hexyne give predominantly the 1,1-diboranyl derivative (**54**), plus unreacted alkyne.³⁹ The 1,1-disubstituted product is formed because hydroboration of the alkene product competes with reaction of the starting alkyne, but hindered boranes such as 9-BBN or Sia₂BH react faster with alkynes than with vinylboranes⁴⁰ leading to less of the 1,1-disubstituted product. This rate difference is apparent in the reaction of octa-4-ene-1-yne (**55**) with Sia₂BH to give the (*E*,*E*)-dienyl-borane, **56**.³⁹ Unhindered terminal alkenes react with organoboranes faster than do alkynes, or at least competitively, especially with unhindered boranes such as diborane.



Although 9-BBN reacts with terminal alkynes to give the trans-alkenylborane, significant amounts of 1,1-diborane are also formed due to the secondary addition to the alkene mentioned above.⁴¹ Brown suggested this was due to the accessibility of the boron to one face of 9-BBN, which can be corrected by addition of a large excess of the alkyne, which is easily recovered, although this is a poor choice for the hydroboration of expensive alkynes. The alkenylborane derived from 9-BBN is stable enough for isolation and can be conveniently purified, in contrast to most other alkenylboranes. The 9-BBN reagent reacts faster with terminal alkynes⁴² than it does

with internal alkynes, as shown by the conversion of octa-1,4-diyne (**57**) to **58**.³⁸ Terminal alkynes react with boranes to give the trans-alkenylborane and 9-BBN reacts with internal alkynes to give the (*Z*)-alkenylborane (with the alkyl groups cis-).⁴⁰



Catecholborane (36) reacts with alkynes but requires reaction temperatures that are higher than

^{38.} Brown, H.C.; Campbell, Jr., J.B. Aldrichimica Acta 1981, 14, 3.

^{39.} Brown, H.C.; Zweifel, G. J. Am. Chem. Soc. 1961, 83, 3834.

^{40.} Brown, H.C.; Moerikofer, A.W. J. Am. Chem. Soc. 1963, 85, 2063.

^{41.} Brown, H.C.; Scouten, C.G.; Liotta, R. J. Am. Chem. Soc. 1979, 101, 96.

^{42.} Brown, C.A.; Coleman, R.A. J. Org. Chem. 1979, 44, 2328.

those required with alkylboranes, as noted earlier. Phenylethyne, for example, reacts with **36** to give excellent yields of the corresponding vinyl borane in refluxing THF.⁴³ Alkenylborinates derived from catecholborane are usually stable, allowing them to be isolated by distillation or recrystallization.³⁸

With two active hydrogen atoms on boron, thexylborane reacted with two equivalents of 1-nonyne to give primarily (but not exclusively) the *trans-,trans-*dialkenylborane **59**.⁴⁴ Terminal alkynes can be used to generate mixed (alkyl-thexyl-alkynyl) boranes that can be used in other transformations (secs. 5.3, 5.4).⁴⁴ Reaction of monochloroborane etherate with alkynes gives a dialkenylborane.⁴⁵ Significant amounts of the 1,1-diborane are usually formed in reactions with terminal alkynes, but using a 40% excess of the alkyne leads to nearly quantitative yields of the dialkenylborane.⁴⁶ A more attractive alternative is to use dibromoborane•methylsulfide (HBBr₂•SMe₂),⁴⁷ which reacts by simple addition with internal alkynes⁴⁸ but reacts with terminal alkynes to give the dialkenylborane without formation of the 1,1-diborane byproduct.

$$n-C_7H_{15}$$
 H H h_2 h_2 $h-C_7H_{15}$ $h-C_7H_{15}$ $h-C_7H_{15}$

Internal alkynes react with boranes to form the cis-alkenylborane. This, of course, is due to the four-center transition state leading to the vinylborane product. The reaction is selective for the less hindered of the two available alkynyl carbons, due to the steric demands of the hydroboration reagent as well as the size and electronic characteristics of the alkynyl substituents. These results are similar to those observed with alkenes when steric factors are the primary influence on the reaction, but the linear nature of alkynes leads to less selectivity than similar reactions with alkenes. When electronic factors dominate, selectivity in the hydroboration reaction is diminished and mixtures of alkenylboranes are formed.³⁸ The regioselectivity for reaction of several terminal alkynes with hydroboration reagents is shown in Table 5.2.³⁸ The reagent of choice for selectivity in the hydroboration of alkynes depends largely on steric factors with most hydroboration reagents, as seen in Table 5.2.

^{43. (}a) Brown, H.C.; Gupta, S.K. J. Am. Chem. Soc. 1972, 94, 4370; (b) Idem Ibid. 1975, 97, 5249.

^{44.} Zweifel, G.; Brown, H.C. J. Am. Chem. Soc. 1963, 85, 2066.

^{45.} Brown, H.C.; Ravindran, N. J. Am. Chem. Soc. 1976, 98, 1785.

^{46.} Brown, H.C.; Ravindran, N. J. Am. Chem. Soc. 1976, 98, 1798.

^{47. (}a) Kinberger, K.; Siebert, W. Z. Naturforsch., B 1975, 30, 55; (b) Brown, H.C.; Ravindran, N. Inorganic Chem. 1977, 16, 2938.

^{48.} Brown, H.C.; Campbell, Jr., J.B. J. Org. Chem. 1980, 45, 389.

<u>Reagent</u>	$n-C_3H_7 - \overset{a}{C} = \overset{b}{C} - H$		$- \overset{a}{\mathbf{C}} \overset{b}{\mathbf{C}} \cdot \mathbf{H}$		\frown	<i>с</i> -с.с.н		Ph - C = C - H a b	
	<u>a</u>	<u>b</u>	<u>a</u>	<u>b</u>	<u>a</u>	b	<u>a</u>	<u>b</u>	
Diborane	40	60	25	75					
Thexylborane	39	61	19	81					
Disiamylborane	39	61	7	93	9	91	19	81	
Dicyclohexylborane	33	67	8	92	8	92	29	81	
HBBr ₂ •SMe ₂	25	75	4	96	9	91	64	36	
9-BBN	22	78	4	96	4	96	65	35	
^a The labels a and b denote the point of attachment of the boron.									

 Table 5.2.
 Directive Effects for Hydroboration of Substituted Internal Alkynes^a

An alternative route to vinylborinates adds the dimethyl sulfide complex of HBBr₂ to 1-bromo-1-alkynes. Reaction of 1-bromo-1-hexyne (**60**) gave **61** in 87% yield after treatment with an alcohol (2-propanol in this case).⁴⁹ Subsequent reduction of the bromide with potassium triisopropoxyborohydride [KBH(O*i*-Pr)₃] generated cis-vinylborane (**62**) in 89% yield.



5.3. SYNTHETIC TRANSFORMATIONS

Sections 5.1 and 5.2 described methods for preparing organoboranes and discussed the regio- and stereo-selectivity associated with their formation from alkenes and alkynes. The synthetic value of organoboranes, however, lies in their ability to serve as intermediates for the transformation of alkenes and alkynes into other useful functional groups. The discussion will begin with the reactions of organoboranes to generate functional groups that do not contain heteroatoms. Heteroatom functional groups will be discussed in Sections 5.4-5.5.

5.3.A. Protonolysis

Alkylboranes react with oxygen and are pyrophoric (the lower alkylboranes burn with a green flame). The product of this reaction is an alkylborinate (R₂BOR). Although tri-*n*-butylborane (and higher analogs) do not spontaneously burst into flame, they are sensitive to oxygen and hydroboration reactions should be protected from air.⁵⁰ Exceptions are 9-BBN and catecholborane, which are much less reactive with oxygen. This sensitivity to oxygen stands in contrast to the relative insensitivity of alkylboranes to water and alcohol. The reaction of

^{49.} Brown, H.C.; Imai, T. Organometallics 1984, 3, 1392.

^{50.} Reference 2, p 67.

trimethylborane, for example, requires 180°C for 7 h to give only 69% of dimethylborinic acid.⁵¹ Not only is the reaction with water, alcohols or phenols slow, addition of aqueous alkali actually stabilizes trialkylboranes to hydrolysis.⁵² Alkylboranes can be hydrolyzed with aqueous mineral acids, but only under vigorous conditions. Conversion of tri-*n*-butylborane to di-*n*-butylboronic acid (**64**) required heating with 48% HBr at reflux,⁵³ and proceeded through the intermediate bromoborane **63**.

$$\overset{Bu}{\underset{Bu'}{\overset{B-n-C_4H_9}{\longrightarrow}}} \xrightarrow{48\% \text{ HBr}}_{\text{reflux, 1 h}} \xrightarrow{Bu} \overset{Bu}{\underset{Bu'}{\overset{B-Br}{\longleftarrow}} + n-C_4H_{10}} \xrightarrow{H_2O} \xrightarrow{Bu} \overset{Bu}{\underset{Bu'}{\overset{B-OH}{\longrightarrow}} + HBr}$$

A more useful method for protonolysis is the reaction of alkylboranes and carboxylic acids at temperatures near 100°C.⁵⁴ In a typical reaction, two of the alkyl groups of the trialkylborane are removed at ambient temperature on treatment with propionic acid.⁵⁵ The yields of hydrocarbon derived from the alkyl portion of the borane are excellent, but protonolysis of the third alkyl group often requires refluxing in diglyme.⁵⁵ Primary alkyl groups undergo protonolysis faster than secondary alkyl. Protonolysis proceeds even in the presence of oxygen, nitrogen, chlorine or sulfur substituents. The mechanism of protonolysis begins with coordination of the boron to the carbonyl oxygen of the acid, followed by transfer of hydrogen to the carbon of the alkyl group via six-center transition state **65**.⁵⁶ Synfacial transfer of hydrogen leads to retention of configuration for transfer of boron to oxygen and hydrogen to carbon, leading to R–H and **66**. This retention of configuration during the reaction is easily observed in the reaction of tri-*exo*-norbornyl-borane (**67**) with refluxing deuteropropionic acid. The product is *exo*-deuteronorbornane (**68**), where the transfer of deuterium proceeded with complete retention of configuration.⁵⁷

$$Me - CO_{2}H \xrightarrow{BR_{3}} \begin{bmatrix} R \\ 0 \\ Me \\ 0 \\ 0 \\ H \end{bmatrix} \xrightarrow{Me} \xrightarrow{O} B^{R} + R - H \qquad (\begin{array}{c} 0 \\ 0 \\ 0 \\ R \\ 0 \\ H^{3} \\ 67 \\ 68 \\ H \\ 67 \\ 68 \\ H \\ 68 \\$$

The protonolysis reaction is sensitive to steric effects, presumably in the transition state (see **65**), as seen in organoborane **70**, formed by hydroboration of (+)- Δ^2 -carene (**69**).⁵⁸ Protonolysis with glacial acetic acid at room temperature *failed* to give carane (**71**), and heating the borane

55. Brown, H.C.; Murray, K. J. Am. Chem. Soc. 1959, 81, 4108.

^{51.} Ulmschneider, D.; Goubeau, J. Berichte 1957, 90, 2733.

^{52.} Reference 2, p 63.

^{53. (}a) Johnson, J.R.; Snyder, H.R.; Van Campen, Jr., M.G. J. Am. Chem. Soc. 1938, 60, 115; (b) Reference 2, p 63.

^{54. (}a) Meerwein, H.; Heinz, G.; Majert, H.; Sönke, H. *J. Prakt. Chem.* **1936**, *147*, 226; (b) Goubeau, J.; Epple, R.; Ulmschneider, D.; Lehmann, H. *Angew. Chem.* **1955**, *67*, 710.

^{56.} Reference 2, p 66.

^{57.} Brown, H.C.; Murray, K.J. J. Org. Chem. 1961, 26, 631.

^{58.} Cocker, W.; Shannon, P.V.R.; Staniland, P.A. J. Chem. Soc. C 1967, 485.

in refluxing acetic acid gave 16 different products.⁵⁹ The failure of the reaction is due to the increased steric bulk around the boron, inhibiting transfer of the hydrogen. This result contrasted with the reaction of the borane of (+)- Δ^3 -carene (double bond between C3 and C4 leading to the product with the boron at C4), which reacted with propionic acid at 150°C to give carane in 45% yield.⁶⁰



Protonolysis of alkenylboranes to generate an alkene is faster than protonolysis of alkylboranes.⁶¹ Once again, protonolysis proceeds stereospecifically with retention of configuration. In Unelius and co-worker's synthesis of 9,11-hexadecadienal isomers from female pheromone glands of the sugar cane borer *Diatraea saccharalis*,⁶² hydroboration of the alkyne unit in **72** with dicyclohexylborane (THF, -20°C) was followed by protonolysis with glacial acetic acid to give a 68% yield of **73**, after oxidation of the dicyclohexylborinate with NaOH/H₂O₂. As with alkylboranes, protonolysis of vinylboranes with deuteroacetic acid allows the synthesis of deuterated alkenes.

$$\begin{array}{c} & & & \\ & & & & \\ & & & \\ & & & \\ &$$

The functional group transforms pertinent to protonolysis are

$$H \xrightarrow{R} \Box \xrightarrow{R} R \xrightarrow{R} H \xrightarrow{R} R \xrightarrow{R}$$

5.3.B. Halogenation

If boron of an alkylborane could be replaced with a halogen, the product would be an alkyl halide. However, reaction of alkylboranes (neat) with chlorine, bromine or iodine is very difficult.^{53a} When halogenation is done with bromine or iodine dissolved in dichloromethane, however, the

^{59.} Acharya, S.P.; Brown, H.C. J. Am. Chem. Soc. 1967, 89, 1925.

^{60.} Brown, H.C.; Suzuki, A. J. Am. Chem. Soc. 1967, 89, 1933.

^{61.} Brown, H.C.; Zweifel, G. J. Am. Chem. Soc. 1961, 83, 3834

^{62.} Santangelo, E.M.; Coracini, M.; Witzgall, P.; Correa, A.G.; Unelius, C.R. J. Nat. Prod. 2002, 65, 909.

reaction is fast and is synthetically useful.⁶³ A simple example is the reaction of alkenes with a borane followed by addition of bromine, which leads to the alkyl bromide. 2-Bromobutane (**78**) was prepared from 2-butene in 88% yield via hydroboration-bromination.⁶⁴ Bromination occurs by a free radical mechanism. Initial reaction of the trialkylborane with bromine generates a bromine radical (Br•), bromoborane (**74**), and 2-butyl radical (**75**). Subsequent reaction with tri-*sec*-butylborane generates the radical at the carbon α to the boron (**76**), and reaction with bromine generates the observed products, **78** and **74**.⁶³ There are many cases where an organoborane does not react very



well with bromine, but addition of bases such as sodium hydroxide or sodium methoxide catalyzes the reaction, allowing it to proceed at temperatures as low as 0°C.⁶⁵ With this modification, formation of bromides (such as **78**) and iodides via hydroboration is synthetically useful. Hydroboration of norbornene initially gives the exo-borane (**67**), but subsequent reaction with bromine and the borane is slow. Addition of NaOMe converts **67** to an *ate* complex (**79**), which rapidly reacts with bromine to give endo-2-bromonorbornane (2-bromobicyclo[2.2.1] heptane, **80**) in 75% yield.⁶⁶ It is interesting to note that the halogenation reaction proceeds with net inversion of configuration at the carbon bearing the boron, suggesting backside attack by bromine. Formation of the *ate* complex and reaction with bromine involves ionic intermediates, not free radical intermediates as noted in reactions of **79**.



Halogenation of vinylboranes generates vinyl halides, and modification of the reaction conditions can lead to either cis or trans halides. When *E*-alkenyl boronic acid (**81**, derived from 1-octyne) was treated with iodine and sodium hydroxide, *E*-1-iodo-1-octene (**82**) was formed in 90% yield.⁶⁷ When the boronic acid was treated with iodine and then with base,

67. Brown, H.C.; Hamaoka, T.; Ravindran, N. J. Am. Chem. Soc. 1973, 95, 5786.

^{63.} Lane, C.F.; Brown, H.C. J. Am. Chem. Soc. 1970, 92, 7212.

^{64.} Lane, C.F.; Brown, H.C. J. Organomet. Chem. 1971, 26, C51.

^{65. (}a) Brown, H.C.; Rathke, M.W.; Rogic, M.M. J. Am. Chem. Soc. **1968**, 90, 5038; (b) Brown, H.C.; Lane, C.F. J. Am. Chem. Soc. **1970**, 92, 6660.

^{66.} Brown, H.C.; Lane, C.F. J. Chem. Soc. Chem. Commun. 1971, 521.

the (*Z*)-alkenyl iodide (83) was produced.⁶⁸ Vinylboranes derived from internal alkynes lead to cis-trans mixtures with both of these procedures. Boronic acids derived from alkynes and catecholborane give the (*Z*)-bromide on addition of bromine followed by sodium hydroxide.⁶⁹

There is an alternative method for converting alkynes to vinyl iodides using B-iodo-9-BBN.⁷⁰ This transformation is illustrated in a synthesis of alcyonin by Overman and co-workers, in which the alkyne unit in **84** was treated with this reagent.⁷¹ Subsequent protonolysis gave an 80% yield of **85**. Note that Piv = pivaloyl. This procedure is more direct and avoids some potential problems with previous procedures.



The halogenolysis reaction makes possible the following transformations:



5.3.C. Alkene, Diene, and Alkyne Synthesis

Vinylboranes are versatile intermediates and there are modifications that convert them to alkenes. Hydroboration of a terminal alkyne such as cyclohexylacetylene (**86**) with dicyclohexylborane gave (*E*)-alkenylborane (**87**). Subsequent treatment with iodine and sodium hydroxide resulted in transfer of an alkyl group from boron to the alkenyl carbon, generating *cis*-1,2-dicyclohexylethene (**88**) in 77% yield (92% isomeric purity)].⁷² Although iodine and base are used, the product is an alkene and not a vinyl iodide. The difference in reaction conditions for halogenation and elimination are subtle, and care must be taken to direct the reaction one way or the other. Conversion to the alkene is believed to proceed via initial coordination of base to

^{68.} Reference 10, p 51.

^{69.} Brown, H.C.; Hamaoka, T.; Ravindran, N. J. Am. Chem. Soc. 1973, 95, 6456.

 ⁽a) Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* 1983, 24, 731; (b) For preparation of B-iodo-9-BBN, see Brown, H.C.; Kulkarni, S.U. J. Organomet. Chem. 1979, 168, 281.

^{71.} Corminboeuf, O.; Overman, L.E.; Pennington, L.D. Org. Lett. 2003, 5, 1543.

^{72.} Zweifel, G.; Arzoumanian, H.; Whitney, C.C. J. Am. Chem. Soc. 1967, 89, 3652.

the boron (to form an *ate* complex), followed by formation of an iodonium (or halonium) ion. This positively charged intermediate facilitates a $1,2-B \rightarrow C$ alkyl shift, which is followed by trans elimination of iodine and boron.¹⁰ A major limitation to this procedure is that it is useful only with symmetrical dialkylboranes. Mixed boranes such as those formed from thexylborane and alkynes lead to migration of both the thexyl group and the alkyl group, giving isomeric mixtures. Halogenation can compete with the elimination reaction as expected, which led to development of an alternative cis-alkene synthesis illustrated by the reaction of 4-octyne and 9-BBN. The product of this reaction was *cis*-4-octene in 98% yield, after protonolysis in refluxing methanol.⁷³ *cis*-4-Octene was also obtained (in 99% yield) in < 15 min at 25°C if 1% acetic acid was added to the reaction.



Manipulation of a vinylborane can lead to trans-alkenes. Hydroboration of a 1-bromoalkyne, followed by treatment with base to induce the B \rightarrow C alkyl shift and then protonolysis gives the trans alkene.⁷⁴ The conversion of 1-bromo-1-hexyne (**60**) to **89** shows that the borane may have alkyl groups different from those found in the alkyne starting material. Treatment with sodium methoxide induced rearrangement to **90**, and protonolysis with acetic acid gave the final product (*E*)-1-cyclohexyl-1-hexene (**91**). In both of these alkene syntheses, the B \rightarrow C alkyl shift proceeded with retention of configuration.⁷⁵ Both alkene-forming reactions have been used for the synthesis of prostaglandin intermediates that relied on the stereoselectivity of the processes.



The dimethyl sulfide complex of chlorothexylborane (see **93**) can be used to generate alkenes from alkynes. Alkenes and alkynes are coupled using this reagent, as illustrated by the reaction of *O*-acetylpent-4-en-1-ol (**92**) and **93**, which gave chloroborane **94** as the initial product. Subsequent reaction with potassium triisopropoxyborohydride (KIPBH) generated an *ate* complex, which reacted with 1-iodo-1-butyne to give **95**. Treatment with sodium methoxide followed by protonolysis gave *trans*-5-octenyl ethanoate (**96**).⁷⁶ An alternative synthetic route to

^{73. (}a) Brown, H.C.; Molander, G.A.J. Org. Chem. 1986, 51, 4512; (b) Brown, H.C.; Wang, K.K. Ibid. 1986, 51, 4514.

^{74.} Zweifel, G.; Arzoumanian, H. J. Am. Chem. Soc. 1967, 89, 5086.

^{75.} Zweifel, G.; Fisher, R.P.; Snow, J.T.; Whitney, C.C. J. Am. Chem. Soc. 1971, 93, 6309.

^{76.} Brown, H.C.; Lee, H.D.; Kulkarni, S.U. J. Org. Chem. 1986, 51, 5282.

(E)-alkenes from alkenyldialkyl-boranes has been developed using cyanogen bromide (BrCN).77



Related techniques have been developed to prepare (Z,Z)-, (Z,E)-, and (E,E)-dienes. Hydroboration of diacetylenes followed by protonolysis gives (Z-,Z)-dienes, as in the conversion of **97** to **98**.⁷⁸ The requisite symmetrical diacetylenes are prepared by oxidative coupling with oxygen and cuprous chloride, as in the conversion of 1-cyclohexylethyne (**86**) to **97**.⁷⁹ Unsymmetrical conjugated dienes are prepared by formation of a diacetylene *ate* complex, prepared from disiamylmethoxyborane by sequential reaction with different acetylides.⁸⁰ Unsymmetrical diynes are prepared from dicyclohexyl methylthioborane.⁸¹



(*E*,*E*)-Dienes are prepared by a different route. Hydroboration of a 1-chloroalkyne such as 1-chloro-1-hexyne (**99**) with thexylborane gives addition product **100**. Treatment of **100** with 1-hexyne leads to a second addition to give alkyldialkenylborane **101**,⁸² and reaction with sodium methoxide leads to a B \rightarrow C shift and **102**. Protonolysis generated the (*E*-,*E*)-diene [**103**, (*5E*,*7E*)-dodecadiene].⁸² Since two alkyne units are incorporated in different steps, this technique is suitable for the preparation of both symmetrical and unsymmetrical dienes. An alternative route to symmetrical (*E*,*E*)-dienes involves treatment of dialkenylchloroboranes with methylcopper^{83a,48} or by a Suzuki-Miyara-type coupling (sec. 12.7.C) in which a vinylboronic acid is coupled to a vinyl iodide in the presence of a palladium (0) catalyst.^{83b} Dienes can also be prepared from dialkyl-alkenylboranes⁸⁴ by reaction with sodium methoxide and then cuprous bromide-dimethyl sulfide (CuBr•SMe₂).

^{77.} Zweifel, G.; Fisher, R.P.; Snow, J.T.; Whitney, C.C. J. Am. Chem. Soc. 1972, 94, 6560.

^{78.} Zweifel, G.; Polston, N.L. J. Am. Chem. Soc. 1970, 92, 4068.

^{79.} Campbell, I.D.; Eglinton, G. Org. Synth. Coll. Vol V 1973, 517.

^{80.} Sinclair, J.A.; Brown, H.C. J. Org. Chem. 1976, 41, 1078.

^{81.} Pelter, A.; Hughes, R.J.; Smith, K.; Tabata, M. Tetrahedron Lett. 1976, 4385.

^{82.} Negishi, E.; Yoshida, Y. J. Chem. Soc. Chem. Commun. 1973, 606.

^{83. (}a) Campbell, Jr., J.B.; Brown, H.C. *J. Org. Chem.* **1980**, 45, 549; (b) For an example used in a synthesis of (-)-dictyostatin, see Ramachandran, P.V.; Srivastava, A.; Hazra, D. *Org. Lett.* **2007**, *9*, 157.

^{84.} Campbell, Jr., J.B.; Brown, H.C. J. Org. Chem, 1980, 45, 550.



(*Z*-,*E*)-Dienes can be prepared by the reaction of alkynes with dibromoborane. Initial reaction of 1-hexyne with the dimethyl sulfide complex of HBBr₂ required addition of boron tribromide (BBr₃) to give the borane that was free of dimethyl sulfide.⁸⁵ In a subsequent reaction with additional 1-hexyne, divinylborane (**104**) was formed and then treated with iodine/acetic acid to give bromodiene (**105**). Addition of *tert*-butyllithium led to bromine-lithium exchange, leading to the vinyllithium reagent (secs. 8.5.A, 8.5.B), and quenching with MeOH gave **106**.



(*Z*,*Z*)-Dienes can be formed. Reaction of 1-bromo-1-hexyne (**60**) and the complex HBBr₂•SMe₂ was followed by reaction with potassium triisopropoxyborohydride to form vinylborane **107**. Subsequent coupling with *cis*-1-bromo-1-octene gave the (*Z*,*Z*)-diene (**108**) in 87% (>99% *ZZ*).⁸⁶ Internal alkynes can also be coupled to give dienes using this procedure,⁸⁷ and terminal alkynes lead to (*E*,*Z*)-dienes, although the regioselectivity of this latter reaction is poor.^{87,88} Two different alkynes can also be coupled to form unsymmetrical dienes.⁸⁹

$$Bu \longrightarrow Br \xrightarrow{1. HBBr_2 \bullet SMe_2} Br \xrightarrow{Bu & Br} \xrightarrow{1. KHB(Oi-Pr)_3} Bu \xrightarrow{n-C_6H_{13}} Oi-Pr \xrightarrow{1. KHB(Oi-Pr)_3} Bu \xrightarrow{n-C_6H_{13}} Oi-Pr \xrightarrow{1. KHB(Oi-Pr)_3} Bu \xrightarrow{n-C_6H_{13}} Oi-Pr \xrightarrow{1. KHB(Oi-Pr)_3} Oi-$$

A synthetic route to unsymmetrical alkynes has been reported, which essentially couples an alkene to a terminal alkyne.⁹⁰ Reaction of chlorothexylborane (93) and 1-octene gave 109 and quenching with methanol gave 110. An *ate* complex (111) was generated when this borane

^{85.} Hyuga, S.; Takinami, S.; Hara, S.; Suzuki, A. Tetrahedron Lett. 1986, 27, 977.

^{86.} Miyaura, N.; Satoh, M.; Suzuki, A. Tetrahedron Lett. 1986, 27, 3745.

^{87.} Brown, H.C.; Ravindran, N.R. J. Org. Chem. 1973, 38, 1617.

^{88.} Zweifel, G.; Polston, N.L.; Whitney, C.C. J. Am. Chem. Soc. 1968, 90, 6243.

^{89.} Zweifel, G.; Backlund, S.J. J. Organomet. Chem. 1978, 156, 159.

^{90.} Sikorski, J.A.; Bhat, N.G.; Cole, T.E.; Wang, K.K.; Brown, H.C. J. Org. Chem. 1986, 51, 4521.
reacted with 1-lithio-1-hexyne. Subsequent iodination and oxidation led to a 75% yield of 5-tetradecyne (**112**).⁹⁰ Two alkyne byproducts were formed, however, resulting from transfer of different alkyl groups to carbon and causing isolation problems for the alkyne of interest. A limitation⁹¹ is due to the observation that different alkyl groups are transferred from species such as **111** to give mixtures of alkyne products.



The variety of reactions illustrated in this section shows the range of alkyne-diene transforms.



5.3.D. Coupling, Isomerization, and Displacement

Organoboranes can be used as synthetic intermediates to make carbon-carbon bonds. As a practical matter, this reaction couples two alkene moieties. Both symmetrical and unsymmetrical coupling products can be formed, although the method is most useful for symmetrical coupling. Initial hydroboration is followed by treatment with basic silver nitrate (AgNO₃) to oxidatively remove boron from the molecule with concomitant coupling of the two alkyl fragments. A typical example is taken from the hydroboration of 2-methyl-1-pentene, which gave the symmetrical coupling product 4,7-dimethyldecane (**113**) in 61% yield after treatment with silver nitrate and NaOH.⁹² The reaction probably proceeds via an alkyl silver intermediate. When this reaction is applied to two different alkenes such as RCH=CH₂ and R¹CH=CH₂, and statistical coupling leads to a mixture of RCH₂CH₂CH₂CH₂R¹.⁹³ This process is useful for the preparation of large, symmetrical alkanes.



^{91.} Pelter, A.; Drake, R.A. Tetrahedron Lett. 1988, 29, 4181.

^{92.} Brown, H.C.; Snyder, C.H. J. Am. Chem. Soc. 1961, 83, 1002.

^{93.} Brown, H.C.; Verbrugge, C.; Snyder, C.H. J. Am. Chem. Soc. 1961, 83, 1001.

Another variation in the hydroboration sequence uses allylic halides to generate cyclic alkanes. Reaction of 9-BBN with allyl chloride generated the ω -chloroborane 114. Treatment with hydroxide initially gave 115, and loss of cyclopropane (formed by internal displacement of chloride) generated the byproduct, 116.⁹⁴ Variations of this process can generate many different substituted and functionalized cyclopropane derivatives. If propargyl bromides are used rather than allylic chlorides, cyclopropylboranes can be formed.⁹⁵ Extending the methylene spacer between the alkynyl moiety and the halide (or other leaving group such as tosyl, mesyl, etc.) allows larger rings to be generated in like manner. The constraint against forming rings of eight atoms and larger (secs. 1.5.B, 6.6.B) is a limiting factor. In more recent work, dienes were coupled to form cyclic compound using 9-BBN, followed by treatment with a palladium catalyzed reaction to give a 42% yield of benzylcyclopentane (118).⁹⁶



The functional group transformations seen in this section lead to the interesting transforms:

5.4. FORMATION OF OXYGEN-CONTAINING FUNCTIONAL GROUPS

5.4.A. Oxidation of Boranes to Alcohols

Perhaps the most utilized transformation of organoboranes is their oxidation to alcohols, accomplished with basic hydrogen peroxide (H_2O_2 , NaOH). The *active* reagent is the hydroperoxide anion (HOO⁻). The overall transformation (alkene \rightarrow alcohol) occurs with an anti-Markovnikov orientation (the OH group is on the less substituted carbon of the C=C moiety) due to the stereochemical preference of the initial hydroboration. This is important, because both the acid catalyzed addition of water to an alkene and oxymercuration (sec. 2.10.A,B) proceed via a cation to give the Markovnikov product. The two-step hydroboration-oxidation sequence is the preferred method for conversion of alkenes to the less substituted

^{94.} Brown, H.C.; Rhodes, S.P. J. Am. Chem. Soc. 1969, 91, 2149.

^{95.} Brown, H.C.; Rhodes, S.P. J. Am. Chem. Soc. 1969, 91, 4306.

^{96.} Lei, A. Zhang, X. Org. Lett. 2002, 4, 2285.

alcohol.² Oxidation of the alkylborane with basic hydrogen peroxide proceeds by initial attack at the boron to give an *ate* complex (**119**), followed by a rapid $B \rightarrow O$ alkyl shift to form borinate **120**. Additional hydroperoxide anion reacts to transfer the other R groups, generating **121**. Final hydrolysis liberates the alcohol.⁹⁷ An example is the conversion of 1-methylcyclopentene to trans-trialkylborane (**122**). Oxidation with basic hydrogen peroxide gave *trans*-2-methylcyclopentanol (**123**) in 86% yield.⁹⁸ The conversion of **124** to **125**⁹⁹ shows that substituted alkenes react faster than more substituted alkenes.



The mechanism shown above implies that the oxidative rearrangement (the $B \rightarrow O$ shift) proceeds with complete retention of configuration at the boron-bearing carbon, as in the conversion of **122** to **123**. For retention to occur the hydroperoxide anion must attack boron rather than carbon, to be followed by a synfacial migration of the alkyl group to oxygen, without rearrangement, epimerization or racemization. Conversion of an alkene to an alcohol in this manner is most efficient when all three of the groups on the trialkylborane are the same, as with **122**. Oxidation will give three equivalents of the alcohol. When 9-BBN or disiamylborane are used in hydroboration reactions, the trialkylborane being oxidized has at least two sites for formation of a C–OH bond. Reaction of 1-heptene with 9-BBN, for example, generated **126** and oxidation generated not only the desired 1-heptanol, but also 1,5-cyclooctanediol (**127**). Separation of these two alcoholic products can be a problem, which limits the utility of hydroboration reactions. The mono-alcohol may be distilled from the mixture, but chromatographic separation of the mono-alcohol from the diol is usually required.

⁽a) Kuivila, H.G. J. Am. Chem. Soc. 1954, 76, 870; (b) Idem Ibid. 1955, 77, 4014; (c) Kuivila, H.G.; Wiles, R.A. Ibid. 1955, 77, 4830; (d) Kuivila, H.G.; Armour, A.G. Ibid. 1957, 79, 5659; (e) Wechter, W.J. Chem. & Ind. (London) 1959, 294

^{98.} Zweifel, G.; Brown, H.C. Org. React. 1964, 13, 1.

^{99.} Chen, L.; Gill, G.B.; Pattenden, G.; Simonian, H. J. Chem. Soc. Perkin Trans. 1 1996, 31.

If disiamylborane were used rather than 9-BBN, the trialkylborane intermediate (**128**) would generate 1-heptanol as well as 2 equivalents of 3-methyl-2-butanol. The separation of the desired alcohol (1-hexanol in this case) from the mono-alcohol byproduct (3-methyl-2-butanol in this case) is potentially more difficult that separating **127** and heptanol. The choice to convert an alkene to an alcohol via hydroboration requires that one weigh the factors of selectivity and reactivity against the ease of isolating the targeted product. When the alcohol product contains many carbons and functional groups, as is common in natural products, the separation problem is probably minimal and selectivity is the major concern. With lower molecular weight alcohol products, ease of isolation may outweigh small increases in selectivity and diborane is probably the reagent of choice.



This alcohol-forming hydroboration reaction is highly regioselective, and sometimes diastereoselective.¹⁰⁰ In a synthesis of amphidinolide T3 Zhao and co-workers reacted **129** with a borane•dimethyl sulfide complex, which led to incorporation of the OH group on the less substituted carbon (an 83% yield of alcohol **130**).¹⁰¹ Note the high regioselectivity, even with borane. Substituted boranes such as disiamylborane, thexylborane or 9-BBN are used in an identical manner, but generally show significantly higher regioselectivity for the less substituted position of the alkene. The alkene unit in **131**, for example, reacted with 9-BBN to give the borane and oxidation gave an 87% yield of **132**, in a synthesis of dolabelide D by Leighton and co-workers.¹⁰² Note that PMB is *p*-methoxybenzyl.



^{100.} Evans, D.A.; Sacks, C.E.; Whitney, R.A.; Mandel, N.G. Tetrahedron Lett. 1978, 727.

^{101.} Deng, L.-S.; Huang, X.-P.; Zhao, G. J. Org. Chem. 2006, 71, 4625.

^{102.} Park, P K.; O'Malley, S.J.; Schmidt, D.R.; Leighton, J.L. J. Am. Chem. Soc. 2006, 128, 2796.

MOLECULAR MODELING: Hydroboration of Flexible Molecules

As illustrated in the previous problem, there are situations where simply looking at a 3D model of the reactant is sufficient to reliably anticipate the favored (kinetic) product of a reaction. This is something that chemists do all the time using "plastic" models, often with considerable success. There are two underlying assumptions. The first is that the transition state for the reaction will "resemble" the products, or that the Hammond Postulate is valid. The second is that the reaction is sterically controlled.

The situation is complicated and prediction more difficult if the reactant is not rigid. Here it is necessary to first establish its conformation. A good example is provided by the hydroboration reaction shown below, which leads with good regio and stereoselectivity to a single alcohol containing three stereocenters. It is reasonable to assume that the boron adds to the less-substituted carbon, meaning that reactions leading to only two (of four possible products) need to be seriously considered. However, the reactant incorporates several (rotatable) single bonds and may exist in a variety of conformations. Each of the presents district "top" and "bottom" faces of the double bond to the hydroboration reagent.



Steric effects (if indeed these are what is in control) depend on detailed conformation, and without knowledge of conformation. Guessing the conformation of a complex reactant is something that plastic models are ill equipped to do. Conformational energy differences are likely to be very small and may arise because of subtle differences in non-bonded intramolecular interactions. Guessing the preferred conformation of the transition states in a reaction such as hydroboration is likely to be even more difficult, as differences in intermolecular interactions also need to be taken into account. However, quantum chemical calculations are well suited for this purpose, and are able to furnish conformations, detailed geometries and (most important) relative energies of transition states leading to different products.

Transition-state modeling is beyond the capability of *SpartanModel* (it is a common application of *Spartan and Spartan Student*). However, models generated by these programs can be shown and queried by *SpartanModel*. Shown on screen are the lowest-energy conformation transition states for addition of borane onto the "top" and "bottom" faces of the alkene shown above. Examine them as space-filling models, and make your best guess as to which is favored. Is this an obvious choice? In fact, the transition state leading to the observed product is 8 kJ/mol lower in energy than the other transition state (corresponding to a room-temperature kinetic product ratio of 95:5). Which transition state shown leads to the major product? Is this the product that is actually observed? However, we can look at results.

Cyclization is an interesting reaction of alkylboranes not discussed in Section 5.3. When the alkyl portion of the borane contains a carbon at the C5 position and when an intermediate dialkylborane possess a B–H bond, cyclization occurs upon vigorous heating (typically 200-

 400° C).¹⁰³ Hydroboration of 2,4,4-trimethyl-1-pentene gave **133**, and heating to 200°C led to 3,3,5-trimethylborinane (**134**). In general, oxidation of borinanes leads to a diol product. The reaction of **134** with basic H₂O₂ gave an 80% yield of 2,2,4-trimethyl-1,5-pentanediol (**135**).¹⁰³

When alkynes are subjected to the hydroboration-oxidation sequence, the alcohol product is actually an enol, and it tautomerizes to a carbonyl derivative (a ketone from internal alkenylboranes and an aldehyde from terminal alkenylboranes). An example is taken from Marshall and Schaaf's synthesis of leptofuranin D,¹⁰⁴ in which the reaction of alkyne **136** with dicyclohexylborane gave vinylborane **137**. Subsequent oxidation gave the enol (**138**), which tautomerized to produce aldehyde **139**, in 95% yield. The synthesis of aldehydes requires that the hydrolysis solution be buffered to pH 7 to minimize condensation reactions of aldehydes (e.g., the **aldol condensation**, sec. 9.4.A). The reaction is regioselective with the position of the carbonyl fixed by the position of the boron in the initially formed alkenylborane. A variation of this reaction uses 1-trimethylsilylalkynes and hydroboration and oxidation leads to a silylketone, which gives a carboxylic acid upon treatment with basic hydrogen peroxide.¹⁰⁵



Cyclic boranes can also be used to generate alcohols in a chain extension reaction. The length of the chain is controlled by the ring size of the borinane. B-Methoxyborinane (140a) reacted with 1-lithio-1-octyne to give an *ate* complex (141a). Iodination and oxidation cleaved the borinane to give 22% of alkynyl alcohol 142.¹⁰⁶ A similar reaction with B-triphenylmethoxyborinane (140b) gave 142 in 85% yield.¹⁰⁶ A variation of this sequence couples cyclic boranes with

^{103.} Reference 2, pp 50-55.

^{104.} Marshall, J.A.; Schaaf, G.M. J. Org. Chem. 2003, 68, 7428.

^{105.} Zweifel, G.; Backlund, S.J. J. Am. Chem. Soc. 1977, 99, 3184.

^{106.} Brown, H.C.; Basavaiah, D.; Bhat, N.G. J. Org. Chem. 1986, 51, 4518.

iodoalkynes, leading to acyclic alkenyl alcohol products.¹⁰⁷ Another chain extension reaction uses diazosilylalknes. The reaction of styrene with catecholborane at 100°C gave **143**. Subsequent reaction with Me₃SiCHN₂ gave **144** and oxidation in the usual manner gave silyl alcohol **145**. Tetrabutylammonium fluoride removes the silyl group, giving 3-phenyl-1-propanol (**146**) in 60% overall yield from styrene.¹⁰⁸



The functional group transformations possible with these reactions are:

5.4.B. Asymmetric Hydroboration

Optically active products can be produced via hydroboration if an optically active borane is used and if the C=C moiety of the alkene precursor is prochiral (sec. 1.4.E). Brown and others developed several chiral alkylboranes by reaction of borane or achiral organoboranes with naturally occurring chiral alkenes such as pinene or longifolene. These chiral organoboranes react to give hydroboration products with good diastereoselectivity and asymmetric induction. The most common synthetic application is to prepare chiral alcohols from alkenes, using diisopinocampheylborane (14, Ipc₂BH) or monoisopinocampheylborane (147, IpcBH₂) derived from α -pinene (6), as well as dilongifolylborane (148, Lgf₂BH), which is derived from longifolene 149.¹⁰⁹ A ligand containing phosphorus and nitrogen groups was used in rhodium-catalyzed asymmetric hydroboration reactions.¹¹⁰

^{107. (}a) Basavaiah, D. *Heterocycles* 1982, 18, 153; (b) Brown, H.C.; Basavaiah, D.; Singh, S.M.; Bhat, N.G. J. Org. Chem. 1988, 53, 246; (c) Brown, H.C.; Basavaiah, D.; Kulkarni, S.U.; Bhat, N.G.; Vara Prasad, J.V.N. *Ibid.* 1988, 53, 239; (d) Brown, H.C.; Basavaiah, D.; Singh, S.M. Synthesis 1984, 920.

^{108.} Goddard, J.-P.; Le Gall, T.; Mioskowski, C. Org. Lett. 2000, 2, 1455.

^{109.} Brown, H.C.; Jadhav, P.K.; Mandal, A.K. Tetrahedron 1981, 37, 3547.

^{110.} Kwong, F.Y.; Yang, Q.; Mak, T.C.W.; Chan, A.S.C.; Chan, K.S. J. Org. Chem. 2002, 67, 2769



Diisopinocampheylborane is prepared by reaction of either(*R*)- or (*S*)- α -pinene (**6**) with diborane,¹¹¹ and this dialkylborane product exists largely as a dimer. The product can also be formed by slow reaction of borane and pinene (3 days in THF) with the major isomer precipitating from solution.^{107a} This chiral non-racemic reagent reacts with alkenes in the usual manner to give a chiral, non-racemic alcohol after oxidation with basic hydrogen peroxide. Hydroboration of an alkene (**150**) occurs from the less hindered side of the molecule via cis addition (to give **151**), and the oxidation proceeds with complete retention of configuration (to give **152**). The stereogenic center of the newly formed alcohol usually has the *opposite* chirality relative to the organoborane [(–)-IpC₂BH gives the (*R*)-alcohol and (+)-IpC₂BH gives the (*S*)-alcohol].¹⁰⁹ Hydroboration of *cis*-2-butene with (*S*)-**14**, for example, gave (*R*)-(–)-2-butanol with 87% ee (in diglyme; 78% ee in THF). Typical percentage asymmetric induction (% ee) for the synthesis of several alcohols using (-)-**14** are: 87% ee (*R*) when R¹=R²=Me, R³=H; 13% (*R*) when R¹=R²=R³=Me; 30% (*R*) when R¹=H, R²=*i*-Pr, R³=Me; and, 48% (*R*) when R¹=R²=H, R³=propyl.¹⁰⁹

Hydroboration of cis alkenes using **14** leads to an alcohol with higher enantioselectivity than obtained from trans alkenes or hindered terminal alkenes. This can be explained by examination of two proposed structures where the borane approaches the alkene in the hydroboration step (see model **153** for cis alkenes and **154** for trans alkenes.¹⁰⁹ The lowest energy conformation for the reagent positions the two pinanyl rings orthogonal to each other, as shown. When a cis alkene approaches, the favored transition state will minimize all steric interactions. The chirality of the pinanyl rings dictates approach from the right face (as drawn in structures **153-156**). If the chirality of this reagent were the opposite of that drawn, approach would be from the left face. The orientation of the alkene is also important in determining enantioselectivity, and this orientation is largely dictated by steric interactions of the alkyl groups on the alkene with one pinanyl ring. The second pinanyl ring is effectively on the other side of the borane, and out of the way of the groups on the alkene. If the alkene approaches from only one face

 ⁽a) Brown, H.C.; Yoon, N.M. Israel J. Chem. 1977, 15, 12; (b) Brown, H.C.; Ayyangar, N.R.; Zweifel, G. J. Am. Chem. Soc, 1964, 86, 397.

(here the right face), there is a pocket that can accommodate groups on the alkene. In **153**, *cis*-2-butene approaches the right face of the pinanyl reagent and is oriented so that the methyl groups are down. This orientation minimizes steric interactions between the methyl groups and the pinanyl group that is on top of the pinanyl reagent (top and bottom are relative in this discussion since the pinanyl borane reagent possesses C_{2v} symmetry). Approach from the same face but with the methyl groups up as in **155** has a greater steric interaction with the bridging methylene unit, and is disfavored relative to **153**. Therefore, this particular representation suggests the **153** should be the model used to predict stereochemistry for cis alkenes.



MOLECULAR MODELING: Addition of a Chiral Borane to cis-2-Butene

Quantum chemical models are actually at their best when called on to elaborate the effects that subtle changes in structure have on both thermodynamic and kinetic product distributions, most commonly changes in regio and/or stereochemistry. Even though energy differences are likely to be small, comparisons among closely related molecules (or transition states) are most likely to benefit from cancellation of errors. Because practical quantum chemical models involve severe approximations to the Schrödinger equation, the *absolute values* of some calculated quantities may show large errors. Reaction and activation energies, in particular, that result from differencing large numbers (total energies) of dissimilar molecules, are prone to large errors. However, energy differences among products of the reaction that differ only subtly (or energy differences among the transition states leading to these products) are likely to be quite well described, simply because deficiencies in the theoretical model will exist in all of the molecules.

A good example is provided by the hydroboration of cis-2-butene using (–)-diisopinocampheylborane as the hydroboration reagent.



MOLECULAR MODELING: Addition of a Chiral Borane to *cis*-2-Butene, con't.

Calculated transition states illustrate the two ways the alkene can approach from a single face, leading eventually to *R* and *S* enantiomers of 2-butanol. The two transition states differ in energy 25 kJ/mol which means that the dominant stereoisomer makes up more than 99% of the total. What is the dominant stereoisomer? Examine both transition state models. Can you point to any differences in the two transition states (steric or otherwise) that would make one better than the other? Elaborate. Suggested reading: Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *Tetrahedron*, *1981*, *37*, 3547.

When *trans*-2-butene reacts with the pinanyl borane reagent, approach from one face leads to a situation where one methyl group is up and interacts sterically with the pinanyl ring, but the other methyl group is down and in a pocket (see 154). The steric interaction of the single methyl group in 154 is greater than the interactions observed in 153, but somewhat similar to those observed in 155. The trans alkene should therefore show poorer selectivity than the cis alkene. Rotation of *trans*-2-butene by 180° along the C=C bond axis (to give 156) exposes the opposite face of the alkene, and also brings one methyl group up and in close proximity to the boranylpinane group that protrudes on top in 156, which suggests that 156 is not significantly lower in energy in 154. No orientation that leads to significantly less severe steric interactions for trans alkenes, as was the case with cis alkenes, and enantioselectivity is poorer for the hydroboration-oxidation sequence. If the two substituents on the trans alkene are sufficiently different in size, however, increased selectivity for reaction at the less sterically hindered carbon is possible. With 1,1-disubstituted alkenes, there is little selectivity in the hydroboration-oxidation sequence. Diisopinocampheylborane apparently forms a trimer rather than react with a severely hindered alkene, which further complicates the reaction.¹⁰⁹ When the borane intermediate of the initial alkene reaction is treated with O-sulfonylhydroxylamine (sec. 5.5.A), enantioselectivity in the chiral amine product is similar to that observed in the alcohol forming sequence.¹⁰⁹ Partridge and Uskoković used diisopinocampheylborane for the conversion of methylcyclopentadiene to 157, in a synthesis of loganin.¹¹²

$$Me \xrightarrow{1. (+)-Ipc_2BH} HO \xrightarrow{Me} 157$$

^{112.} Partridge, J.J.; Chadha, N.K.; Uskoković, M.R. J. Am. Chem. Soc, 1973, 95, 532.

MOLECULAR MODELING: Stereochemistry of Addition of a Chiral Borane

Previous problems have suggested the difficulty of assigning product distributions using structure models, even models derived from accurate quantum chemical calculations. A further illustration is provided here. Reaction of 5-methylcyclopentadiene with (–)-diisopinocampheylborane, followed by oxidation leads predominately to alcohol **157**. This is one of four possible products and corresponds to approach of boron at C_1 *anti* to the methyl group.



The four transition states appear on screen: C_1 anti product (top left), C_2 anti product (top right), C_2 syn (lower right) and C_1 anti (lower left). Examine the four both as ball-and-spoke and spacefilling models. Based on these models, can you rationalize the fact that the transition state at the top left is 9 kJ/mol lower in energy than any of the other transition states? Hint: Focus your attention on the methyl group of the five-membered ring, and the relationship of the five-membered ring to the pendant pinanyl rings. Elaborate. Guess the identity of the next lowest-energy transition state. From this guess, are you able to conclude that in this case, *syn/anti* selectivity is more or less important than positional selectivity?

Asymmetric induction has been observed in the hydroboration of heterocyclic rings such as dihydrofuran, dihydropyrrole, dihydropyran or dihydrothiophenes.¹¹³ In a typical example, dihydrofuran **158** gave a 92% yield of **159** with 100% ee R.¹¹³ Note that these reactions required addition of acetaldehyde to displace α -pinene prior to oxidation of the borane. Dihydropyrrole **160** gave **161** in 92% yield and 89% ee *S*, without the need to use acetaldehyde.¹¹³ These cases show that the hydroboration reaction is highly regioselective for placement of the boron on the alkene carbon distal to the heteroatom. Tetrahydropyridine derivative **162**, however, gave an 85:15 mixture of **163** and **164** in 68% yield, and **163** was formed with 70% ee R.¹¹³

^{113.} Brown, H.C.; Vara Prasad, J.V.N. J. Am. Chem. Soc. 1986, 108, 2049.



Monoisopinocampheylborane (147) is another important chiral borane formed by reaction of α -pinene with the triethylamine complex of thexylborane¹¹⁴ to give the monoisopinylcamp hylborane•triethyl-amine complex. It is necessary to release monoisopinocampheylborane by treatment with borane•THF or boron trifluoride etherate.¹¹⁵ This reagent is obviously less hindered than the diisopinocampheyl derivative and reacts faster, even with hindered and polysubstituted alkenes. The highest enantioselectivity is observed with trans alkenes (see 165). When R¹=R³=Me, R²=H, for example, 167 was formed with 72% ee.¹⁰⁹ The cis alkene (R¹=R²=Me, R³=H,), however, gave 167 in only 24% ee.¹⁰⁹ Initial reaction with 165 generates a chiral organoborane (166), and oxidation gives the alcohol (167) with retention of configuration.

$$\underset{R^{1}}{\overset{H}{\underset{R^{2}}}} \xrightarrow{R^{2}} \overset{IpcBH_{2}}{\underset{R^{2}}{\overset{H}{\underset{R^{2}}}} \xrightarrow{R_{2}B} \overset{H}{\underset{R^{3}}{\overset{H}{\underset{R^{3}}}} \xrightarrow{H}} \overset{H}{\underset{R^{3}}{\overset{H}{\underset{R^{2}}}} \xrightarrow{NaOH} \overset{HO}{\underset{H_{2}O_{2}}{\overset{H}{\underset{R^{3}}}} \xrightarrow{HO} \overset{H}{\underset{R^{3}}{\overset{H}{\underset{R^{3}}}} \xrightarrow{R^{2}}$$

Asymmetric induction increases with increasing steric demands of the alkene, but cis alkenes show the *worst* selectivity. This can be explained by three-dimensional drawing **168**, which shows approach of one face of *cis*-2-butene with the two methyl groups *exo*- to the pinanyl ring (when the methyl groups are *endo*- there is a steric interaction). Rotating *cis*-2-butene by 180° along the axis that *bisects* the C=C bond (C=/=C) exposes the other face of the alkene. This representation clearly suggests no facial bias for the cis alkene and, little or no enantioselectivity in the hydroboration reaction. Examination of **169a** for interaction of one face of *trans*-2-butene with the pinanyl borane reagent shows that the methyl groups occupy "pockets" with minimal steric hindrance. Rotation of 2-butene by 180° along the axis that *bisects* the C=C bond (C=/=C) exposes the opposite face (**169b**), and the steric interaction with the bridging methylene unit is rather severe. These representations suggest a facial bias for the

^{114. (}a) Brown, H.C.; Yoon, N.M.J. Am. Chem. Soc. 1977, 99, 5514; (b) Brown, H.C.; Schwier, J.R.; Singaram, B.J. Org. Chem. 1978, 43, 4395; (c) Brown, H.C.; Yoon, N.M.; Mandal, A.K.J. Organomet. Chem. 1977, 135, C10.

^{115.} Brown, H.C.; Mandal, A.K. Synthesis 1978, 146.

trans-alkene that is not present for the *cis*-alkene, and good enantioselectivity for trans alkenes. 2-Butene shows outstanding selectivity because it is symmetrical. Unsymmetrical alkenes show good selectivity only when there are significant differences in the size of substituents. 1,1-Disubstituted alkenes show good selectivity *if* both groups are large, and particularly if one group is significantly larger than the other.



Although 14 shows good selectivity for cis alkenes and 168 shows good selectivity for transalkenes, no reagent showed good selectivity with both cis and trans alkenes. A solution to this problem was found when dilongifolylborane (148) was prepared by reaction of the dimethyl sulfide complex of borane with (+)-longifolene (149), which is readily available [the (–) antipode is rare however].¹¹⁶ Compound 148 is a dimeric, high-melting white crystalline solid that is stable in ether solvents and can be stored several weeks without decomposition. This reagent gives good enantioselectivity with both cis and trans alkenes, as well as 1,1-disubstituted alkenes.¹⁰⁹ *cis*-2-Butene reacted with 148 to give the alcohol with 78%ee and 2-methyl-2-pentene gave the corresponding alcohol with 75 %ee.¹⁰⁹ The selectivity can be explained with model 170, which shows the approach of *cis*-2-butene to 148, and reveals that cis alkenes can be accommodated if small to moderately sized substituents are present. Good selectivity is also observed in reactions with 1,1-disubstituted alkenes. Borane 148 also accommodates trans alkenes, as seen in 171 for approach of *trans*-2-butene, where selectivity increases as the steric size increases.



^{116.} Jahhav, P.K.; Brown, H.C. J. Org. Chem. 1981, 46, 2988.

Alkene	<u>Reagent (0°C, THF)</u>	<u>Time (h)</u>	<u>Alcohol</u>	<u>% Yield</u>	<u>% ee</u>
cis-2-Butene	2-ICr ₂ BH	12	2-Butanol	63	93 (S)
	4-Icr ₂ BH	72		58	50 (R)
trans2-Butene	2-ICr ₂ BH	150		69	30 (R)
	4-Icr ₂ BH	72		62	40 (S)
2-Methyl-1-butene	2-ICr ₂ BH	3	2-methyl-1-butanol	61	15 (S)
	4-Icr ₂ BH	4		72	5 (R)
2-Methyl-2-butene	2-ICr ₂ BH	240	3-Methyl-2-butanol	61	37 (S)
, in the second s	4-Icr ₂ BH	120	5	75	Ó
trans-3-Hexene	4-Icr ₂ BH	72	3-Hexanol	65	32 (<i>S</i>)
1-Methylcyclopenter	ne 2-ICr ₂ BH	240	2-methylcyclopentanol	65	3 (<i>RR</i>)
	4-Icr ₂ BH	26		72	3 (<i>RR</i>)
[Reprinted with permission from Brown, H.C.; Vara Prasad, J.V.N.; Zaidlewicz, M. J. Org. Chem. 1988, 53, 2911. Copyright © 1988 American Chemical Society.]					

 Table 5.3.
 Asymmetric Hydroboration with Carene Based Reagents

Another class of chiral boranes has been prepared from Δ^2 -carene (**69**) and Δ^4 -carene (**173**) and the first widely used reagents are (1*S*)-di-2-isocaranylborane (**172**, 2-^dIcr₂BH) and (1*S*)-di-4isocaranylborane (**174**, 4-^dIcr₂BH).¹¹⁷ These reagents behave in a similar manner to Ipc₂BH but are less reactive, and their relative reactivity is: Ipc₂BH > 2^dIcr₂BH > 4-^dIcr₂BH. Table 5.3¹¹⁷ illustrates the selectivity and asymmetric induction of **172** and **174** upon reaction with a variety of alkenes. These reagents showed good selectivity with cis alkenes but trans alkenes and terminal alkenes react slowly and show poor selectivity.



The five reagents discussed in this section show that chiral boranes can induce moderate to good enantioselectivity in the conversion of alkenes to alcohols (or to amines, sec. 5.5.A). These reagents are a powerful addition to the growing list of enantioselective reactions used in organic synthesis.

5.4.C. Addition of Allylboranes to Carbonyl Compounds

A particularly useful borane is the chiral reagent (–)-B-allyl(diisopinocampheyl)borane.¹¹⁸ Although the chemistry of acyl addition to aldehydes and ketones to give alcohols will not be formally discussed until Section 8.4.C, the addition of this chiral allylborane to carbonyl compounds will be presented here. In a synthesis of peloruside A by Zhou and Liu ,¹¹⁹ **175**

^{117.} Brown, H.C.; Vara Prasad, J.V.N.; Zaidlewicz, M. J. Org. Chem. 1988, 53, 2911.

^{118.} Brown, H.C.; Jadhav, P.K. J. Am. Chem. Soc. 1983, 105, 2092.

^{119.} Liu, B.; Zhou, W.-S. Org. Lett. 2004, 6, 71.

was treated with (–)-B-allyl(diisopinocampheyl)borane in ether at -78 °C. The usual oxidation gave **176** in good yield.



Enantioselectivity in this reaction is usually excellent, but substitution on the alkylborane can diminish diastereoselectivity, as with crotylborane derivatives. This is not always the case, however. In a synthesis of (–)-dictyostatin by Ramachandran, and co-workers,¹²⁰ treatment of **177** with two equivalents of (*E*)-(+)-crotyldiisopinocampheylborane followed by an oxidative workup, gave **178** in good yield as a single diastereomer.

t-BuMe₂SiO CHO
$$1.$$
 $B(Ipc)_2$ t -BuMe₂SiO 177 t -BuMe₂SiO 178 OH

Although this reaction is used most often with aldehydes, other carbonyl compounds can be used. It is known that carboxylic acids,¹²¹ esters,^{121a,b,122} anhydrides¹²² or amides¹²² react with allylic boranes to give the corresponding alcohols. In one example, 2-pyrrolidinone reacted with triallylborane to give a 90% yield of 2,2-diallylpyrrolidine (**179**) after treatment with methanol followed by basic hydrogen peroxide.¹²³ This transformation is believed to proceed by initial addition to the carbonyl followed by elimination to give an imine. The imine reacts with a

second equivalent of triallylborane to give the 2,2-disubstituted derivative. The methanol cleaves the N-B bond and the oxidation step removes the remaining borane derivatives.



The disconnection for this reaction is

The reader is also directed to Section 12.7.C for a palladium-catalyzed coupling reaction involving boronic acids called **Suzuki-Miyaura coupling**.

^{120.} Ramachandran, P.V.; Srivastava, A.; Hazra, D. Org. Lett. 2007, 9, 157.

⁽a) Mikhailov, B.M.; Bubnov, Yu.N.; Tsyban, A.V.; Grigoryan, M.Sh. J. Organomet. Chem. 1978, 154, 131; (b) Mikhailov, B.M.; Bubnov, Yu.N.; Tsyban, A.V. Izv. Akad. Nauk, Ser. khim. 1978, 1892; (c) Bubnov, Yu.N.; Demina, E.E.; Bel'sky, V.K.; Zatonsky, G.V.; Ignatenko, A.V. Izv. Akad. Nauk, Ser. khim. 1998, 2320.

^{122.} Kramer, G.W.; Brown, H.C. J. Org. Chem. 1977, 42, 2292.

^{123.} Bubnov, Y.N.; Pastukhov, F.V.; Yampolsky, I.V.; Ignatenko, A.V. Eur. J. Org. Chem. 2000, 1503.

5.4.D. Oxidation to Aldehydes and Ketones

The alcohols that were formed via hydroboration and oxidation in Section 5.4.A can be oxidized to aldehydes or ketones with an appropriate oxidizing agent (see Chap. 3) after they are isolated from the hydroboration-oxidation sequence. It is possible to combine these steps and oxidize organoboranes directly to ketones by treatment with chromic acid. Hydroboration of cyclohexene, for example, generated tricyclohexylborane and oxidation with chromic acid rather than basic hydroperoxide gave a 65% yield of cyclohexanone directly. Initial oxidation of tricyclohexylborane likely gave the alcohol, which was oxidized to the ketone (cyclohexanone) *in situ*.¹²⁴ The oxidation to the alcohol proceeds by a chromate ester of boron and the rate of oxidation is sensitive to steric effects,¹²⁵ analogous to the chromic acid oxidation of secondary alcohols (sec. 3.2.A). Using diethyl ether as a solvent facilitates isolation of the final ketone product. When the alkyl substrate is sensitive to acid rearrangement, chromic acid oxidation can facilitate that rearrangement.¹²⁶ As with oxidation of organoboranes to form alcohols, there

are many synthetic examples. In Harmata and Bohnert's synthesis of sterpurene, hydroboration of alkene **180** followed by oxidation with pyridinium chlorochromate gave a 66% yield of ketone **181**.¹²⁷



A direct synthesis of aldehydes involves hydroboration of terminal alkynes. In a synthesis of bafilomycin,¹²⁸ Marshall and Adams first converted the alkyne unit in **182** to the vinylborane unit in **183** using dicyclohexylborane. Subsequent oxidation generated the corresponding enol, and tautomerization gave aldehyde **184** in 81% yield. This sequence converts terminal alkynes to the aldehyde.



Ketones or tertiary alcohols can be prepared from organoboranes using cyano *ate* complexes. Ketone formation requires transfer of two alkyl groups from the boron. Treatment of tri-*n*-butylborane with sodium cyanide (NaCN) gave the cyano *ate* complex (**185**). An electrophilic reagent such as trifluoroacetic anhydride [(CF₃CO)₂O] was added to initiate migration of the alkyl groups from boron to carbon, allowing oxidation with basic hydrogen peroxide to give

^{124.} Brown, H.C.; Garg, C.P. J. Am. Chem. Soc. 1961, 83, 2951, 2952.

^{125.} Ware, J.C.; Traylor, T.G. J. Am. Chem. Soc. 1963, 85, 3026.

^{126.} Lansbury, P.T.; Nienhouse, E.J. J. Chem. Soc. Chem. Commun. 1966, 273.

^{127.} Harmata, M.; Bohnert, G.J. Org. Lett. 2003, 5, 59.

^{128.} Marshall, J.A.; Adams, N.D. J. Org. Chem. 2002, 67, 733.

the symmetrical ketone, 5-nonanone in 94% yield.¹²⁹ Treatment of the cyano-*ate* complex with sodium hydroxide and then basic hydrogen peroxide in the usual oxidation sequence leads to a tertiary alcohol. Tri-*n*-butylborane was converted to 5-butyl-5-nonanol in 85% yield along with a 15% yield of 5-nonanone by this procedure.¹³⁰



The mechanism of tertiary alcohol formation is postulated to be initial formation of an imine such as **187** from the cyano *ate* complex (**186**). Cyclization via attack at boron in **187** led to **188**, which was opened by reaction with trifluoroacetate anion to give **189**. Oxidation of **189** gave the tertiary alcohol, **190**. The ketone product is formed by oxidation of the intermediate **188**, although oxidative cleavage of **189** is also possible.¹³¹

$$\begin{array}{c} R \\ R \\ R' \\ CN \\ R' \\ CN \\ \hline R' \\ R' \\ \hline R'$$

While this method is best suited for the preparation of symmetrical alcohols or ketones, formation of unsymmetrical ketones is difficult unless selective transfer of the alkyl groups can be achieved. Thexylborane provides a solution since it can react sequentially with two different alkenes to generate an unsymmetrical trialkylborane. Reaction of thexylborane with cyclopentene and then arylalkene **191**, for example, gave **192**. Subsequent reaction with sodium cyanide gave the unsymmetrical *ate* complex (**193**), which gave unsymmetrical ketone **194** upon treatment with trifluoroacetic anhydride followed by oxidation.^{130b}

^{129.} Pelter, A.; Hutchings, M.E.; Smith, K.G. J. Chem. Soc. Chem. Commun. 1970, 1529.

 ⁽a) Brown, H.C.; Nambu, H.; Rogić, M.M. J. Am. Chem. Soc. 1969, 91, 6852; (b) Pelter, A.; Smith, K.; Hutchings, M.G.; Rowe, K. J. Chem. Soc. Perkin Trans. 1 1975, 129; (c) Pelter, A.; Hutchings, M.G.; Rowe, K.; Smith, K. Ibid. 1975, 138.

^{131.} Pelter, A.; Hutchings, M.G.; Smith, K. J. Chem. Soc. Chem. Commun. 1971, 1048.



Cyclic ketones can be formed by the hydroboration of dienes, followed by the oxidation sequence just described. In a typical example, taken from Bryson and Welch's synthesis of confertin, **195** was first reacted with the ylborane in the presence of sodium cyanide to give **196**. Subsequent treatment with trifluoroacetic anhydride and then oxidation with basic hydrogen peroxide gave a 70:30 mixture of **197** and **198** in 48% yield.¹³² This **boron annulation sequence** has been applied to the synthesis of several bicyclic alkaloids.¹³³



The functional group transforms for the alkene to ketone conversion are:



5.4.E. Carbonylation: Formation of Alcohols, Aldehydes and Ketones

There is an alternative method for converting organoboranes into alcohols or carbonyl derivatives that requires more vigorous reaction conditions. Organoboranes react with CO in a reaction that transfers the three alkyl groups of a trialkylborane from boron to carbon,¹³⁴ but this transformation requires relatively high pressures of carbon monoxide as well as high temperatures (typically 70 atm and 150°C) to form intermediate **199**. Subsequent oxidation induces the usual $B \rightarrow O$ shift in **199**, which leads to a symmetrical tertiary alcohol (**200**). A simple example of this reaction involves the reaction of tricyclohexylborane (from cyclohexene) with CO to give **199** (R = cyclohexyl), and oxidation generated tricyclohexylcarbinol (**200**, R

- 133. Garst, M.E.; Bonfiglio, J.N. Tetrahedron Lett. 1981, 22, 2075.
- 134. Brown, H.C. Acc. Chem. Res. 1969, 2, 65.

^{132.} Welch, M.C.; Bryson, T.A. Tetrahedron Lett. 1988, 29, 521.

= cyclohexyl) in an overall yield of 86%.¹³⁵

$$\begin{array}{c} R \\ B-R \\ R' \end{array} \xrightarrow{CO (70 \text{ atm})} R \xrightarrow{R} \\ 150^{\circ}C \end{array} \xrightarrow{R-C} B-O \xrightarrow{NaOH} R \xrightarrow{R} \\ R \\ R' \end{array} \xrightarrow{R-C} OH \\ R \\ 199 \end{array}$$

This sequence is useful for the preparation of symmetrical tertiary alcohols, even highly hindered ones that would be difficult to prepare by other routes. It is limited to an organoborane derived from a single alkene, however, since a mixed borane will lead to several alcohol products. Hydroboration of dienes and trienes lead to cyclic, bicyclic or tricyclic tertiary alcohols. The method is illustrated by reaction of diborane with 1,5,9-cyclododecatriene (**201**), which gave tricyclic borane **202** that has a bridgehead boron. Carbonylation and oxidation as before incorporate the carbon group and led to the tricyclic alcohol (perhydrophenalenol, **203**)¹³⁶ where the carbinol carbon bridges all three rings. This compound was produced in 70% yield in three chemical steps, and would be difficult to prepare by other synthetic methods.



Another route to tertiary alcohols involves monomethylborane (MeBH₂), which can be prepared from lithium methylborohydride (LiMeBH₃).¹³⁷ Reaction of MeBH₂ with two equivalents of 1-hexene gave **204**. Carbonylation and oxidation gave a 1:1 mixture of **205** and **206**.¹³⁷ When ten equivalents of 1-hexene were used and the hydroboration was done at –25°C (in THF), carbonylation and oxidation gave **205** in 96% yield.¹³⁷ Ketones rather than alcohols can be synthesized if the carbonylation step is done in the presence of water. In this modification, an OH group and two alkyl groups are transferred to carbon. Oxidation leads directly to an intermediate that decomposes to a ketone rather than an alcohol.¹³⁸ Hindered boranes, especially thexylborane, react sluggishly at atmospheric pressure, so a pressure of 70 atmospheres of CO is required. Reaction of thexylborane with cyclopentene gave **207**, and subsequent reaction with *O*-acetyl-hept-6-en-1-ol gave the trialkylborane (**208**). Carbonylation in the presence of water followed by oxidation gave the mixed ketone (**209**) in 73% yield.¹³⁹ In a similar manner,

^{135.} Brown, H.C.; Ratke, M.W. J. Am. Chem. Soc. 1967, 89, 2737.

^{136.} Brown, H.C.; Negishi, E. J. Am. Chem. Soc, 1967, 89, 5478.

^{137.} Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K.-W. J. Org. Chem. 1986, 51, 4925.

^{138.} Brown, H.C.; Rathke, M.W. J. Am. Chem. Soc, 1967, 89, 2738; (b) Brown, H.C.; Dickason, W.C. Ibid. 1969, 91, 1226.

^{139. (}a) Brown, H.C.; Negishi, E. Synthesis 1972, 196; (b) Idem J. Am. Chem. Soc, 1967, 89, 5285.

dienes can be transformed into the corresponding cyclic ketones.^{140,141}



Another modification of the carbonylation sequence adds a single carbon to a substrate and generates an aldehyde. Treatment of 4-vinylcyclohexene (**210**) with 9-BBN, gave the expected borane (**211**). Subsequent carbonylation, in the presence of lithium trimethoxyaluminum hydride [LiAlH(OMe)₃, sec. 4.3], gave an α -boranyl alkoxyaluminate (**212**). Treatment with hydroxide liberated the alcohol (**213**), but oxidation of **212** with buffered hydrogen peroxide gave aldehyde **214**.^{134,142} The reaction of **211** with a complex hydride increased the rate of CO uptake by the trialkylboranes (this is a general phenomenon).¹⁴³ Indeed, a small amount of free trialkylborane must be present in the reaction medium or carbonylation does not occur at a reasonable rate.¹⁴⁴ Trialkylborohydrides are probably the active reducing agents in this reaction.¹⁴⁵ When sodium borohydride or lithium tri-*tert*-butoxyaluminum hydride was used, complex side reactions accompanied carbonylation. For this reaction, lithium trimethoxyaluminum hydride or potassium triisopropoxyborohydride is the preferred reagent.



- 140. Brown, H.C.; Negishi, E. J. Am. Chem. Soc, 1967, 89, 5477.
- 141. Brown, H.C.; Negishi, J. Chem. Soc. Chem. Commun. 1968, 594.
- 142. Brown, H.C.; Knights, E.F.; Coleman, R.A. J. Am. Chem. Soc, 1969, 91, 2144.
- (a) Brown, H.C.; Krishnamurthy, S.; Hubbard, J.L. J. Organomet. Chem. 1979, 166, 271; (b) Brown, H.C.; Krishnamurthy, S.; Hubbard, J.L.; Coleman, R.J. Ibid. 1979, 166, 281; (c) Brown, C.A.; Hubbard, J.L. J. Am. Chem. Soc. 1979, 101, 3964
- 144. Brown, H.C.; Hubbard, J.L. J. Org. Chem. 1979, 44, 467.
- 145. Hubbard, J.L.; Smith, K. J. Organomet. Chem. 1984, 276, C41.

The functional group transforms in this section are quite useful and are outlined below:

5.4.F. Conjugate Addition

Borane, monoalkylboranes and dialkylboranes (such as thexylborane and 9-BBN), all with a B-H unit, are known to be powerful reducing agents for carbonyl derivatives (sec. 4.6.A). When no B-H unit is present, as in trialkylboranes, addition to the alkene moiety of α , β -unsaturated ketones or aldehydes occurs. An alkyl group of the borane is transferred to the terminal position of the alkene moiety (1,4-addition), and boron is transferred to the oxygen, to give a boron enolate (sec. 9.4.D). Initial hydroboration of acrolein with tricyclopentylborane gave boron enolate (sec. 9.4.D). Initial hydroboration of acrolein with tricyclopentylborane gave boron enolate **215**.¹⁴⁶ Hydrolysis of **215** generated an enol and, thereby, aldehyde **216** in 88% yield.¹⁴⁷ Conjugated ketones react in a similar manner to give substituted ketone products.¹⁴⁸ Brown and co-workers noted that the reaction with acrolein was a useful method for the *three-carbon extension* of a carbon chain. It was also observed that the reaction was inhibited by addition of free radical inhibitors such as galvinoxyl, which implies that initial addition to the conjugated system probably proceeded by a free radical chain mechanism.¹⁴⁹



The relatively simple functional group transform for this reaction is:

$$\begin{array}{c} \mathbb{R}^{l} & \longrightarrow & \mathbb{R} \\ 0 & \longrightarrow & 0 \end{array}$$

5.4.G. Carbanions Containing Boron, Boron Enolates, and Enolate-Like Derivatives

Organoboranes react with bromine to form brominated boranes,¹⁵⁰ but they also react with brominated substrates. α -Bromo esters, for example, react with organoboranes to give

^{146.} Brown, H.C.; Rogić, M.M.; Rathke, M.W.; Kabalka, G.W. J. Am. Chem. Soc, 1967, 89, 5709.

^{147.} Brown, H.C.; Kabalka, G.W.; Rathke, M.W.; Rogić, M.M. J. Am. Chem. Soc, 1968, 90, 4165, 4166.

^{148.} Suzuki, A.; Arase, A.; Matsumoto, H.; Itoh, M.; Brown, H.C.; Rogić, M.M.; Rathke, M.W. J. Am. Chem. Soc, 1967, 89, 5708

^{149.} Kabalka, G.W.; Brown, H.C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. J. Am. Chem. Soc. 1970, 92, 710.

^{150. (}a) Brown, H.C.; DeLue, N.R. J. Am. Chem. Soc, 1974, 96, 311; (b) Lane, C.F.; Brown, H.C. J. Am. Chem. Soc, 1971, 93, 1025; (c) Pelter, A.; Smith, K.; Brown, H.C. Borane Reagents, Academic Press, New York 1988, p250.

coupling products if a base is added to the bromination reaction.^{151a} Adding a base suppresses radical bromination, allowing an ionic reaction to predominate. This transformation has been successfully applied to several different classes of molecules, including α -bromoketones, α -chloronitriles, α -bromosulfoxides or 4-bromocrotonates.¹⁰ If phenyl or arylboranes are used as the organoborane partner, bromoesters can be arylated.

If a α -bromo carbonyl compound such as ethyl α -bromoacetate is treated with base, an enolate is formed (secs. 9.2, 9.4.B). The enolate can react with a trialkylborane to give an *ate* complex such as **217**, formed from ethyl bromoacetate and trinorbornylborane (**67**). The *ate* complex rearranges via a B \rightarrow C shift that transfers an alkyl group from boron, replacing the bromine and giving **218**.^{151a} The protonated base (the conjugate acid in this case is *tert*-butanol) generated by the initial enolate forming reaction is a sufficiently strong acid to initiate loss of boron. The resulting enol tautomerizes to ester **219** in 85% yield.^{151a}



The transforms possible by these reactions are



5.5. AMINES AND SULFIDES VIA HYDROBORATION

Both nitrogen and sulfur can be to incorporated into organic molecules by hydroboration. The most common is nitrogen, but there are a few examples where sulfur or even metals have been inserted into organic molecules.

5.5.A. Nitrogen-Containing Compounds

Trialkylboranes are converted to primary and secondary amines in a convenient manner.¹⁵² Chloramine (ClNH₂) or hydroxylamine *O*-sulfonic acid (H₂N-OSO₃H) react with trialkylboranes to give primary amines.¹⁵³ Treatment of tributylborane with either reagent, for example, gave 1-aminobutane (**220**). The reaction proceeds via attack by nitrogen at the boron to give *ate* complex **221**. A B \rightarrow N alkyl shift proceeds with expulsion of the leaving groups (X⁻ or HSO₄⁻), to give **222**, which reacts with a second equivalent of amine to give **223**. Subsequent treatment

^{151. (}a) Brown, H.C.; Rogić, M.M.; Rathke, M.W.; Kabalka, G.W. J. Am. Chem. Soc, 1968, 90, 818, (b) 1911.

^{152.} For a review of synthetic applications, see Carboni, B.; Vaultier, M. *Bull. Soc. Chim. Fr.* **1995**, 132, 1003.

^{153.} Reference 150c, p 252.

with NaOH leads to cleavage and formation of the alkylamine (220). Similar reaction with



hindered organoboranes requires a temperatures of ~ 100°C.¹⁵⁴ Lewis acid can be added to the reaction to facilitate incorporation of the nitrogen by formation of a more labile *ate* complex, and also to promote the requisite $B \rightarrow N$ rearrangement. In a synthesis of potentiators of 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA) receptors,¹⁵⁵ Shepherd and coworkers reacted 1-phenylcyclopentene with chloroborane and then trimethylaluminum to form the corresponding *ate* complex. Finally, treatment with hydroxylamine *O*-sulfonic acid gave the *trans*-amine, **224**. Boranes derived from aromatic compounds usually give poor yields of amines, although this can be improved by using Lewis acids as in the example just described. Lewis acids promote the rearrangement (there is a favorable intramolecular reaction) because of the proximity of the aromatic nucleus to the aminating species. Asymmetric hydroboration is possible in these reactions, giving chiral, nonracemic amines. When styrene was treated with catecholborane in the presence of a chiral rhodium catalyst and then treated with MeMgCl (Et₂Zn can also be used), a complex was formed that generated a chiral borane. Subsequent treatment with H₂NOSO₃H gave a 54% yield of **225** in 87% ee.¹⁵⁶



^{154.} Rathke, M.W.; Inoue, N.; Varma, K.R.; Brown, H.C. J. Am. Chem. Soc. 1966, 88, 2870.

^{155.} Shepherd, T.A.; Aikins, J.A.; Bleakman, D.; Cantrell, B.E.; Rearick, J.P.; Simon, R.L.; Smith, E.C.R.; Stephenson, G.A.; Zimmerman, D.M.; Mandelzys, A.; Jarvie, K.R.; Ho, K.; Deverill, M.; Kamboj, R.K. *J. Med. Chem.* **2002**, *45*, 2101.

^{156.} Fernandez, E.; Hooper, M.W.; Knight, F.I.; Brown, J.M. Chem. Commun. 1997, 173.

^{157.} Levy, L.A.; Fishbein, L. Tetrahedron Lett. 1969, 3773.

^{158.} Mueller, R.H. Tetrahedron Lett. 1976, 2925.

Azides react with trialkylboranes, and the resulting intermediate can be converted to a secondary amine.¹⁵⁹ The initial reaction requires high temperatures, however. In the example shown, the boron in triethylborane is attacked by a nitrogen of phenyl azide (**229**) to form ate complex **230**. A B \rightarrow N shift of an ethyl group generated **231** via expulsion of nitrogen. Methanolysis and oxidation gave the secondary amine (*N*-ethylaniline), in 78% yield.¹⁵⁹ The oxidation step was required only to destroy excess borane. Both alkyl-dichloroboranes¹⁶⁰a and dialkylchloroboranes^{160b} react with azides to give secondary amines. In one example, dichloroborane reacted with 1-methylcyclopentene to give **232**. Subsequent reaction with cyclohexylazide generated a new chloroborane (**233**), and this was treated with aqueous hydroxide to give an unsymmetrical secondary amine (**234**) in 90% yield. The rearrangement and oxidation proceeded with complete retention of the trans geometry in the cyclopentane ring.^{160a} When trialkylboranes react with chlorodimethylamines, the products are tertiary dimethylamines, but a radical scavenger such as galvinoxyl must be added to suppress competing radical reactions.¹⁶¹



A related azide reaction was used to prepare phenylalanine.¹⁶² Chiral borinane **235** reacted with lithium dichloromethane (LiCHCl₂) to give **236**. Subsequent reaction with sodium azide gave **237**. Reaction with a second equivalent of LiCHCl₂ was followed by oxidation with NaClO₂ to give azido acid **238**. Catalytic hydrogenation (sec. 4.8) gave phenylalanine (**239**) in 63% overall yield.¹⁶²



^{159.} Suzuki, A.; Sono, S.; Itoh, M.; Brown, H.C.; Midland, M.M. J. Am. Chem. Soc. 1971, 93, 4329.

162. Matteson, D.S.; Beedle, E.C. Tetrahedron Lett. 1987, 28, 4499.

^{160. (}a) Brown, H.C.; Midland, M.M.; Levy, A.B. J. Am. Chem. Soc. 1973, 95, 2394; (b) Idem Ibid 1972, 94, 2114.

^{161.} Davies, A.G.; Hook, S.C.W.; Roberts, B.P. J. Organomet. Chem. 1970, 23, C11.

5.5.B. Sulfur

Trialkylboranes react with organic disulfides to give thioethers (sulfides), but air or light is required because the reaction proceeds by a radical chain process.¹⁶³ This reaction is very slow in the dark and ultraviolet (UV) light is required for reasonable reaction rates. Trioctylborane

reacts with dimethyl disulfide under these conditions to give methyl 1-octyl sulfide in 95% yield.¹⁶³ The mixed borane, *B*-cyclohexyl-3,5-dimethylborinane (**240**) gave 94% of cyclohexyl methyl sulfide (**241**) under the same conditions.¹⁶³



The preparation of unsymmetrical sulfides is increasingly important since chiral sulfoxides can be prepared (sec. 3.9.A) and used in organic synthesis. α -Lithio sulfides give useful carbanion reactions and sulfur ylids can be formed (secs. 8.6, 8.8.B). The difficulties in preparing primary and secondary amines by traditional methods (from halides or tosylates via reaction with imides or azides, sec. 2.6) make the hydroboration-amination sequence a mild and useful alternative for the synthesis of amines.

The functional group transforms available in this section are

$$R \xrightarrow{\text{NHR}^{1}} R \xrightarrow{\text{R}} R \xrightarrow{\text{CO}_{2}\text{H}} R \xrightarrow{\text{CO}_{2}\text{H}} R \xrightarrow{\text{R}} R \xrightarrow{\text{SMe}} R \xrightarrow{\text{SMe}} R \xrightarrow{\text{SMe}} R$$

5.6. CONCLUSION

This chapter concludes the discussion of functional group exchange reactions commonly used in organic synthesis. Hydroboration provides alternatives to many of the transformations described in chap. 1, and adds many unique ones. Hydroboration also provides new examples of controlling asymmetric induction by proper design of reagents. This idea will be reviewed in chap. 6 and it will include general methods for controlling selectivity. Problems unique to forming cyclic compounds will also be discussed.

HOMEWORK

- 1. Virtually all of the functional group transforms associated with organoboranes involve conversion to an *ate* complex. Explain why this is the case.
- 2. Give the major product of the reaction shown, and discuss all forms of selectivity that apply to it.

^{163.} Brown, H.C.; Midland, M.M. J. Am. Chem. Soc. 1971, 93, 3291.



3. Predict the structure of each product, A-F.

$$A + NH_2OSO_3H \longrightarrow B A + CH_3CO_2D, diglyme, 100°C \longrightarrow C$$

$$A + H_2O_2, KOH \longrightarrow D$$

$$A + I_2, NaOH \longrightarrow E A + (1) CO, H_2O (2) NaOH, H_2O_2 \longrightarrow F$$

4. For each of the following, draw an appropriate transition state and predict the major product(s).

(a) (-)-IpC₂BH + (3Z) hexene (b) (-)-IpC₂BH + 6-methyl-(3E)-octene (c) (+)-IpCBH₂ + (3E)-hexene

- 5. Give three different examples of carbon-carbon bond-forming reactions involving boranes. Show all starting materials, reagents, and product(s).
- 6. Provide a mechanistic rationale for the following transformation:

$$\frac{1. B_2H_6, 165^{\circ}C}{2. NaOH, H_2O_2} \longrightarrow OH$$

7. Provide a rationale for formation of the indicated product, paying particular attention to the stereochemistry of the secondary alcohol.



8. The following transformations are very convenient using a hydroboration strategy. Discuss the possibility of alternative synthetic routes that do <u>not</u> involve hydroboration.



9. Predict the major product of this reaction and justify the stereochemistry of the final product.



10. In each case, give the major product or products. Remember stereochemistry where it is appropriate.



11. Predict the major product. Explain the selectivity of each reaction.



12. In each case, provide a suitable synthesis. Show all reagents and intermediate products.



Stereocontrol and Ring Formation

6.1. INTRODUCTION

6

chapter

Chapters 1-5 contain many examples of regioselective, diastereoselective or enantioselective reactions involving both acyclic and cyclic molecules. Chelating effects with certain heteroatom containing substrates was also discussed, with examples of how chelation control could override the effect of non-bonded interactions. There were examples that illustrated the ability to influence, and sometimes control the facial selectivity of a reaction in both acyclic and cyclic systems. Conformational preferences (orientations) in the substrate were also shown to be important. The purpose of this chapter is to focus attention on methods for either controlling the conformational effects in a molecule, or exploiting unalterable conformational effects to achieve a specific synthetic purpose. This chapter provides a review that will summarize key concepts, and focus attention on stereoselectivity prior to discussing carbon-carbon bond-forming reactions.

Section 6.5 in this chapter will summarize methodology for controlling the stereochemistry of acyclic molecules by taking advantage of the conformational bias of cyclic molecules. The cyclic carrier is chemically modified, and then the ring is opened to give a substituted or functionalized acyclic molecule with a certain stereochemical pattern. Another section deals with intramolecular cyclization reactions for generating small, medium, and large ring compounds. The limitations and synthetic value of these ring forming reactions will also be discussed. This chapter will present the fundamental ways an organic chemist recognizes the conformational and topological features of a molecule, and uses that information to give a desired result. This strategy includes recognition of those molecular features that will prevent the desired reaction or lead to incorrect stereochemistry, allowing the chemist to design alternatives.

6.2. STEREOCONTROL IN ACYCLIC SYSTEMS

Reactions of acyclic molecules can generate stereoisomers, and when a chemist refers to "controlling stereochemistry" in such a reaction there is an attempt to generate one stereoisomer in preference to another as the major product of a reaction. Typical situations where control of stereochemistry is important include: (1) Regioselectivity (Markovnikov versus anti-Markovnikov), (2) Retention versus inversion of configuration, (3) cis-trans Selectivity, (4),

syn-anti Selectivity, and (5) Heteroatom chelation effects.

Reactions where these effects are important were presented in previous chapters. The carboncarbon bond forming reactions in succeeding chapters contain many additional examples. The purpose of this chapter is not to solve specific synthetic problems (diastereoselective enolate alkylation and condensations, selectivity in the Claisen rearrangement, etc.), but rather to define the problems in a general sense. Approaches for solving these problems will be discussed, but specific solutions are usually presented in other chapters.

6.2.A. Regioselectivity

Regioisomers have the same empirical formula, but groups or atoms are positioned at different carbon atoms. 3-Methylhexanal and 4-methylhexanal are regioisomers, for example. A reaction that generates one regioisomer as the major product can be regioselective or regiospecific. We can take an example from one of the fundamental transformations presented in Chapter 2, addition to an alkene. The reaction of 2-methyl-2-butene with HBr gives 2-bromo-2-methylbutane as the major product, a typical Markovnikov addition, so the reaction is highly regioselective. This reaction proceeds by formation of the more stable carbocation, which reacts with the nucleophilic bromide ion (sec. 2.10.A). If the anti-Markovnikov bromide (1-bromo-2-methylbutane) is desired, a different mechanistic pathway must be followed. Reaction of the alkene with HBr and a peroxide proceeds by a radical mechanism, giving 1-bromo-2-methylbutane, the anti-Markovnikov bromide (secs. 2.10.A, 13.5.B).¹

$$HBr \qquad HBr \qquad I. Sia_2BH \qquad OH \qquad PBr_3 \qquad Br \qquad Br \qquad HBr \qquad HBr$$

Understanding which products are formed and the mechanism of their formation, is essential if one is to control which product is formed. Addition of HBr generates a carbocation, with the charge residing on the more substituted carbon. The three alkyl substituents attached to the positive center provide more electronic stabilization to the p orbital of the cation than is possible in the other possible intermediate, the primary carbocation. Reaction of the tertiary carbocation and the nucleophilic bromide ion generates 2-bromo-2-methylbutane as the major product. When a peroxide is added, Br• is generated *in situ* (sec. 13.3) and this radical adds to the alkene to give the more stable radical. This radical intermediate reacts with more HBr to give the anti-Markovnikov product and more bromine radical. If a reaction generates a cation, Markovnikov orientation is sure to result. If anti-Markovnikov addition is desired, *the reaction must proceed by a different reaction mechanism*. The radical mechanism satisfies this requirement and if the reaction generates a radical, anti-Markovnikov orientation is preferred^{2,3} (secs. 13.3-13.6).

^{1. (}a) Markovnikoff, V. Compt. Rend. 1875, 81, 668; (b) Isenberg, N.; Grdinic, M. J. Chem. Educ. 1969, 46, 601.

^{2.} Curran, D.P. Synthesis 1988, 489.

 ⁽a) Keck, G.E.; Yates, J.B. J. Am. Chem. Soc. 1982, 104, 5829; (b) Keck, G.E.; Enholm, E.J.; Yates, J.B.; Wiley, M.R. Tetrahedron 1985, 41, 4079.

Hydroboration of alkenes is another regioselective reaction (see Chap. 5). Addition of borane to the alkene, gives 2-methyl-1-butanol after oxidation of the intermediate alkylborane, a typical anti-Markovnikov addition product (sec. 5.4.A).⁴ The hydroboration-oxidation sequence is highly regioselective for the generating the OH unit on the less substituted carbon atom of the alkene. The hydroboration reaction with alkenes to produce alkylboranes⁴ (sec. 5.2) proceeds by a four-center transition state rather than a cationic intermediate. The regiochemistry of the final alkylborane product is controlled by the non-bonded steric interactions of the groups attached to boron (in this case *sec*-isoamyl from the disiamylborane) and the groups on the alkene. Oxidation with basic hydrogen peroxide converts the borane to the anti-Markovnikov alcohol. With this alcohol in hand, treatment with PBr₃ gives 1-bromo-2-methylbutane, the anti-Markovnikov bromide mentioned above. Once again, understanding the fundamental mechanism of the hydroboration reaction, allowed us to prepare first the anti-Markovnikov alcohol form the alkene, and then convert it to the bromide. It is clear from these examples, that a product with a certain regiochemistry can be synthesized by modifying the chemical reaction to follow a different mechanistic pathway, or by choosing a different chemical synthesis.

6.2.B. Retention versus Inversion of Configuration

Functional group transformations often proceed with retention, racemization or inversion of a stereochemical center, as in the substitution reactions from Chapter 2 (S_N2 and S_N1 , for example). Hydroxylation and dihydroxylation reactions in chapter 3 gave diastereomers or enantiomers, and reduction of ketones and aldehydes in Chapter 4 led to formation of stereoisomeric alcohols. In Chapter 4, Cram's rule or the Felkin-Ahn model allowed one to predict the stereochemistry of the alcohol being formed. Clearly, it is important to predict which stereoisomer is preferred if the reaction is stereoselective, and it is also important to anticipate poor stereocontrol in a reaction. In the S_N2 reaction, we know that the reaction proceeds with complete stereochemical inversion and the S_N1 is predicted to proceed with complete or partial racemization. This section will discuss methodologies that allow one to predict the stereochemical outcome of a reaction, or even to change it after the fact.



A classical example of controlling the configuration of a stereocenter is conversion of a chiral secondary alcohol to the corresponding secondary chloride with thionyl chloride,⁵ and it is also another example of changing stereochemistry by modifying the mechanism of the reaction.

^{4. (}a) Brown, H.C. Hydroboration, W.A. Benjamin, New York, 1962; (b) Idem Pure Appl. Chem. 1976, 47, 49.

 ⁽a) Lee, C.C.; Finlayson, A.J. Can. J. Chem. 1961, 39, 260; (b) Lee, C.C.; Clayton, J.W.; Lee, D.G.; Finlayson, A.J. Tetrahedron 1962, 18, 1395.

Both retention of configuration (neat SOCl₂) and inversion (SOCl₂ + pyridine) are possible (sec. 2.8.A).⁵ Thionyl chloride reacts with (*S*)-2-pentanol to produce a chlorosulfinate ester (**1**). The HCl by-product escapes from the reaction medium, and an intramolecular delivery of chloride in what is called a S_N i mechanism (see 1)^{5,6} gives (*S*)-2-chloropentane (**2**), with concomitant loss of sulfur dioxide (SO₂). The synfacial delivery of chlorine generates the chloride with retention of configuration. If pyridine (or another basic tertiary amine) is added, the HCl by-product is trapped as the pyridinium hydrochloride salt (**3**) and nucleophilic chloride ion is in the medium. Displacement of the chlorosulfinate ester (**1**) by chloride ion, in an S_N 2 reaction, gives chloride **4** with net inversion of configuration.⁷ The stereochemistry of the reaction is, therefore, controlled by the presence or absence of a nucleophilic chloride ion in the reaction medium.



Formation of 4 showed that conversion of the OH unit to a leaving group allows an $S_N 2$ reaction to occur. Indeed, $S_N 2$ displacement is possible with substrates containing many different leaving groups, all with inversion of that stereogenic center. Conversion of (S)-2-pentanol to the corresponding tosylate (5), for example, allows reaction by nucleophiles such as azide to give 6 with complete control of the stereogenic center. Changing the poor leaving group OH to the good leaving group tosylate allows greater flexibility in the synthetic sequence. Changing the leaving group may be ineffective, however, if the nucleophile is too weak. As we saw in Chapter 2, there is a great difference in nucleophilic strength for a given substrate and reaction type. If a nucleophile, such as methoxide, reacts with 5, the $S_N 2$ reaction would give a methyl ether. Nucleophiles such as methoxide are strong bases, however, and elimination can occur to give an alkene via the E2 reaction (sec. 2.9.A). The use of highly polar, aprotic solvents such as DMF or DMSO can sometimes increase the yield of substitution product (secs. 2.7.A, 2.6.A.i) and minimize elimination by-products, just as the use of a protic solvent such as methanol usually increases the amount of elimination products. In planning the reaction, the course of a reaction can be modified by changing the structural components of the substrate (good versus poor leaving group), or by changing the reaction partner and/or the solvent. Clearly, competing reactions must be considered, in addition to the factors that control reactivity and stereochemistry.

$$\underbrace{\overset{H}{\longrightarrow}}_{Me} \underbrace{\overset{O}{\longrightarrow}}_{Py} \underbrace{\overset{O}{\longrightarrow}}_{Me} \underbrace{\overset{O}{\longrightarrow}}_{Me} \underbrace{\overset{N}{\longrightarrow}}_{f} \underbrace{\overset{N}{\longrightarrow}}_{f} \underbrace{\overset{N}{\longrightarrow}}_{Me} \underbrace{\overset{N}{\longrightarrow}}_{f} \underbrace{\overset{N}{\longrightarrow}}_{f} \underbrace{\overset{N}{\longrightarrow}}_{Me} \underbrace{\overset{N}{\longrightarrow}}_{f} \underbrace{\overset{N}{\longrightarrow}}_{$$

If one chooses the substrate, reactants or reaction conditions to favor one mechanism over other possibilities, good stereocontrol may be achieved. The ability to control a stereogenic center

^{6.} Lewis, E.S.; Boozer, C.E. J. Am. Chem. Soc. 1952, 74, 308.

^{7.} Darzens, G. Compt. Rend. 1911, 152, 1601.

using a $S_N 2$ reaction is illustrated by the reaction of (*S*)-bromide **7** with the potassium salt of benzylthiol to give thioether **8**, in 77% yield and 98% ee as part of the Seki et al. synthesis of an orally active 1- β -methylcarbapenam TA-949.⁸ The importance of solvent in this reaction is illustrated by differences in % ee. When THF was used as the solvent, **8** was isolated in only 12% ee. Selectivity was raised to 48% ee in DMF, and to 72% ee when the reaction was done in water.⁸

A successful and highly useful S_N^2 reaction that is commonly used to change the stereochemistry of a reactive center is the **Mitsunobu reaction** (sec. 2.6.A.ii).⁹ The Mitsunobu reaction usually involves mixing diethylazodicarboxylate (DEAD) and triphenylphosphine (Ph₃P) with an alcohol in the presence of nucleophiles.⁹ Other phosphines can be used as well. The Mitsunobu reaction is typically used to invert a stereochemical center, transforming a (*R*)-hydroxyl unit to a (*S*)-hydroxyl unit for example. This process is illustrated by the conversion of **9** to **11**, taken from Hudlicky, Pettit and co-worker's synthesis of narciclasine.¹⁰ **Luche reduction** (sec. 4.4.B) of **9** gave **10** due to the conformational restraints on delivery of the hydride using this reagent. The relative stereochemistry of the hydroxy unit was incorrect for narciclasine, and was corrected by reaction of **10** with DEAD, tributylphosphine and benzoic acid to give benzoate **11**. The benzoate group was later removed to liberate the alcohol with Amberlyst A21 in methanol.¹⁰ Note that other nucleophiles can be incorporated into a molecule using Mitsunobu conditions.



Other methods are available for controlling relative stereochemistry. An example is the $NH_2 \rightarrow Br$ transformation, with complete retention of configuration. Reaction of amino acid **12** with sodium nitrite (NaNO₂) and potassium bromide (KBr) converted the amino group to a bromide, and gave α -bromo acid (**13**) with Me $12^{CO_2H} \xrightarrow{NH_2}_{CO_2H} \xrightarrow{NaNO_2, KBr}_{Me} \xrightarrow{HO}_{Me} \xrightarrow{Br}_{CO_2H}$

^{8.} Seki, M.; Yamanaka, T.; Kondo, K. J. Org. Chem. 2000, 65, 517.

^{9.} Mitsunobu, O. Synthesis 1981, 1.

Hudlicky, T.; Rinner, U.; Gonzalez, D.; Akgun, H.; Schilling, S.; Siengalewicz, P.; Martinot, T.A.; Pettit, G.R. J. Org. Chem. 2002, 67, 8726.

complete retention of configuration,¹¹ a reaction first observed by Walden.^{11b-d} This reaction was taken from Salzmann and co-worker's synthesis of the potent carbapenam antibiotic thienamycin.¹² Note that this is a special case where the carboxylate unit participates in the reaction.by conversion of *D*-mannitol to (*R*)- or (*S*)-epichlorohydrin.¹³ Tosyl diol **14**, obtained from (*D*)-mannitol, was chlorinated selectively at the more reactive primary alcohol to give **15**. Treatment with sodium gave the epoxide (*S*)-epichlorohydrin (**16**).¹³ Reaction of **14** with the basic sodium methoxide, however, generated a hydroxy epoxide via displacement of the tosylate leaving group. Subsequent treatment of the hydroxy epoxide with methanesulfonyl chloride generated the mesylate (**17**). Reaction of the epoxide oxygen with HCl gave chlorohydrin **18**, which gave (*R*)-epichlorohydrin (**19**) upon treatment with sodium methoxide (the OMs in **18** is a better leaving group than Cl). This example shows that understanding reactivity differences in a molecule can lead to control of the stereochemistry in chemical manipulations.



6.2.C. cis-trans Selectivity

Addition of certain reagents to a C=C unit of an alkyne (hydrogenation, addition of halogens, etc.) can lead to either cis- or trans-alkenes. Control of cis-trans-geometry is well illustrated by catalytic hydrogenation or alkali metal reduction of alkynes, as discussed in Sections 4.8.B and 4.9.C, respectively. The Lindlar catalyst (sec. 4.8.B) allows selective hydrogenation of alkynes to the cis-alkene, as in the conversion of **20** to **21** in 78% yield, in studies directed towards the synthesis of discodermolide by Parker and Katsoulis.¹⁴ This contrasts sharply with treatment of an alkyne with alkali metals (sec. 4.9.C) to give the trans alkene, as in the conversion of **22** to **23**.¹⁵ Once again, a fundamental understanding of the difference in these two reaction mechanisms allowed control of the cis-trans geometry of the final product. Control of cis-trans-geometry (diastereoselectivity) in cyclic systems will be discussed in Section 6.3.D.

^{11. (}a) Shimohigashi, Y.; Waki, M.; Izumiya, N. Bull. Chem. Soc. Jpn. 1979, 52, 949; (b) Walden, P. Berichte 1895, 28, 2766; (c) Idem, Ibid. 1896, 29, 133; (d) Idem, Ibid. 1899, 32, 1855.

^{12. (}a) Salzmann, T.N.; Ratcliffe, R.W.; Christensen, B.G.; Bouffard, F.A. J. Am. Chem. Soc. 1980, 102, 6161;
(b) Mellilo, D.G.; Liu, T.; Ryan, K.; Sletzinger, M.; Shinkai, I. Tetrahedron Lett. 1981, 22, 913.

^{13.} Baldwin, J.J.; Raab, A.W.; Mensler, K.; Arison, B.H.; McClure, D.E. J. Org. Chem. 1978, 43, 4876.

^{14.} Parker, K.A.; Katsoulis, I.A. Org. Lett, 2004, 6, 1413.

^{15.} Kochansky, J.P.; Cardé, R.T.; Taschenberg, E.F.; Roelofs, W.L. J. Chem. Ecol. 1977, 3, 419.



Reactive intermediates in several reactions have a C=C unit, and stereochemistry plays a role in the selectivity of those reactions. Two examples are organometallics such as Grignard reagents derived from vinyl halides, and enolate anions. The configurational stability of these species will be discussed in detail in sections 8.4.F, 8.5.D and in Sections 9.2.C, 9.5,

respectively. There are problems associated with cis-trans isomerism. When (1*E*)-bromo-1-propene (24) reacts with magnesium, Grignard reagent 1-propenylmagnesium bromide 25 ($R = CH_3$, R^1



= H, secs. 8.4.A, 8.4.F) is formed. Isomerization led to a mixture of the (*E*)-isomer (**25**) in 60-70% yield with 30-40% of the (*Z*)-isomer (**26**),¹⁶ and this is reflected in the subsequent reactions of the Grignard reagent. In other words, when **25** + **26** react with an aldehyde, the corresponding allylic alcohol product will be a mixture of (*E*)- and (*Z*)-isomers. In general, reaction of trans alkenyl organometallics tend to give the trans alkenyl product, and cis alkenyl halides give the corresponding cis alkenyl product. Isomerization can be a problem in these reactions, however.^{16b}

When a ketone reacts with a suitable base (secs. 9.1, 9.2) an enolate anion is formed by removal of the α -proton. In the case of an unsymmetrical ketone such as 27, a mixture of (Z)-enolate (28) and (E)-enolate (29) will result (secs. 9.2.E, 9.5.A). The diastereoselectivity and enantioselectivity in products formed by enolate condensation reactions (sec. 9.5) are influenced

by the stereochemistry of the enolate anion. When s mixture of geometrical isomers **28** and **29** reacts with aldehydes, a mixture of both syn- and antiproducts will be formed, so it is important to



predict or know the geometry of the enolate anion. Several solutions to this problem have been developed, including formation of stable and separable enolate isomers, and controlling reaction conditions to maximize production of one isomer. These techniques will be discussed in Section 9.2, but an example can be presented here to illustrate the approach. Reaction of 3-pentanone (**27**, R = Et, $R^1 = Me$) with lithium diisopropylamide gave a 77:23 mixture of (*E*)- and (*Z*)-enolate anions.¹⁷ Similar reaction with lithium 2,2,6,6-tetramethylpiperidide

^{16. (}a) Martin, G.J.; Méchin, B.; Martin, M.L. C.R. Acad. Sci., Ser. C 1968, 267, 986; (b) Martin, G.J.; Martin, M.L. Bull. Soc. Chim. Fr. 1966, 1636.

^{17.} Evans, D.A. in Asymmetric Syntheses, Vol. 3, Morrison, J.D. (Ed.), Academic Press, New York, 1984, p16.

(LTMP), gave only slightly greater amounts of the (*E*)-enolate (86:14 *E*/*Z*), but addition of HMPA) to this latter reaction medium led to a reversal of selectivity, favoring the (*Z*)-enolate (8:92). Upon subsequent reaction with a substrate such as another aldehyde or ketone, this (*E*/*Z*)-mixture of enolate anions will give a similar mixture of diastereomers in the products. Some isomerization can occur in the deprotonation or condensation steps, and the product may isomerize under the reaction conditions,¹⁸ as we will see in chapter 9.

6.2.D. syn-anti Selectivity

There are many reactions that generate a mixture of syn and anti diastereomers, and if the reaction is diastereoselective one predominates. Dihydroxylation of alkenes to give a syndiol is one example from chapter 3, and the addition of bromine to an alkene to give an antidibromide is another. Reaction of alkenes with aqueous permanganate or osmium tetroxide (secs. 3.5.A-C) gives a cis diol via the syn hydroxylation mechanism. The reaction is generally diastereoselective for the *cis*-diol, but it is not enantioselective. In synthetic studies aimed at the tricyclic skeleton of natural *Celastraceae* sesquiterpenoids, Barrett and co-workers reacted **30** with a catalytic amount of osmium tetroxide and *N*-methylmorpholine *N*-oxide, giving a 72%% yield of **31a** and **31b** in a 1:1 ratio.¹⁹ Although the reaction was diastereoselective for the *cis*-diol, the lack of enantioselectivity in the presence of the other stereogenic centers led to the mixture.



An alternative method for stereoselectivity generating diols begins with an epoxide (32), formed by oxidation of an alkene (sec. 3.4), which is opened to the diol with hydroxide (or another oxygen nucleophile). In this example, syn diol 33 was formed via backside approach of the nucleophilic hydroxide to the less hindered carbon of 32. Epoxide 32 is assumed to be optically active so the enantiopurity of the diol product can be determined and this is used as a measure of the stereoselectivity of the ring opening. Different mechanistic pathways form diols 31 and 33. Changing to a different mechanistic process can modify the selectivity. Treatment of this epoxide with a catalytic amount of perchloric acid or sulfuric acid (in 90% aqueous DMSO), for example, gave a mixture of cis and trans diols in roughly equal amounts, although there was a slight excess of the trans.²⁰ In this latter case, acid catalyzed ring opening proceeds via a carbocation that reacted with water to give a mixture of diastereomers. When ring opening was initiated by KOH in the nonaqueous environment, an S_N2 like mechanism

^{18.} Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.C.; Sohn, J.E.; Lampe, J.J. Org. Chem. 1980, 45, 1066.

^{19.} Siwicka, A.; Cuperly, D.; Tedeschi, L.; Le Vézouët, R.; White, A.J.P.; Barrett, A.G.M. Tetrahedron Lett. 2007, 48, 2279.

^{20.} Berti, G.; Macchia, B.; Macchia, F. Tetrahedron Lett. 1965, 3421.
led to formation of a single diastereomer via backside attack. In 85% aqueous DMSO, for example, 1-phenyl cyclohexene oxide reacted with KOH to give the trans diol.



6.2.E. Heteroatom Chelation

One major way to control diastereoselectivity is to take advantage of the chelating effect of neighboring heteroatom groups (neighboring group effects) with certain reagents, which can be illustrated by reaction of chiral allylic alcohol **34** with a peroxyacid. Coordination with the oxygen (see **35**) and delivery of the electrophilic oxygen from that side²¹ gave epoxy-alcohol **36** as the major diastereomer, which means that coordination directs the stereochemical course of the reaction. In Chapter 3 and especially in chapter 4, the neighboring group effects of heteroatoms were important for the observed diastereoselectivity in epoxidation, hydride reduction or hydroboration, as well as haptophilic effects in catalytic hydrogenation (sec. 4.8.B).



The **Sharpless asymmetric epoxidation** (sec. 3.4.D.i) exploits a chelation effect, because its selectivity arises from coordination of the allylic alcohol to a titanium complex in the presence of a chiral agent. The most effective additive was a tartaric acid ester (tartrate), and its presence led to high enantioselectivity in the epoxidation.²² An example is the conversion of allylic alcohol **37** to epoxy-alcohol **38** (95% yield, 97% ee), in a synthesis of (–)-apicularen A by Panek and Su.²³ In this reaction, the tartrate, the alkenyl alcohol and the peroxide bind to titanium and provide facial selectivity for the transfer of oxygen from the peroxide to the alkene. Binding of the allylic alcohol to the metal is important for delivery of the electrophilic oxygen and also for controlling orientation of the alkene relative to the epoxidation agent. In this example, coordination with the chiral tartrate led to preferential delivery from the opposite (*si*) face. The reaction is enantioselective and diastereoselective, and syn-anti-selectivity is controlled by the coordination of substrate to the (+) or (–) tartrate.

^{21.} Henbest, H.B. Proc. Chem. Soc. 1963, 159.

^{22. (}a) Katsuki, T.; Sharpless, K.B. J. Am. Chem. Soc. 1980, 102, 5974; (b) Sharpless, K.B.; Verhoeven, T.R. Aldrichimica Acta 1979, 12, 63.

^{23.} Su, Q.; Panek, J.S. J. Am. Chem. Soc. 2004, 126, 2425.

The **Cram chelation model** (sec. 4.7.B) exploits the chelation effects of a heteroatom to influence the rotamer population and, thereby, the selectivity of the reduction. Zinc borohydride $[Zn(BH_4)_2]$ effectively chelates the carbonyl and alcohol oxygen atoms, in the reduction of **39**, and leads to intermediate **40**. Transfer of hydride to the carbonyl gave primarily the anti diastereomer, **42** (4:96, **41/42**). Lithium aluminum hydride shows less selectivity, due in part to poorer coordination with the heteroatom and reduction of **39** gave a 27:73 mixture of **41** and **42**, respectively.²⁴ When the chelating hydroxyl group was blocked as a *tert*-butyldiphenylsilyl ether (in **43**, sec. 7.3.A.i), reduction with Red-Al (sec. 4.3) led to a reversal in selectivity (96:4, **44/45**).²⁴ The chelation ability of a heteroatom varies with the reagent used.



Other heteroatoms can coordinate with reducing agents to afford high selectivity. Reduction of **46** with zinc borohydride, for example, gave a 76:24 mixture of **47** and **48** (61% yield) that was eventually converted by Davis and co-workers to (–)-SS20846A^{25a} [(4*S*)-hydroxy-(2*S*)-(1-pentadienyl)piperidine], a proposed intermediate in the biosynthesis of the potent antimicrobial agent streptazolin.^{25b,c}



^{24.} Nakatu, T.; Yanaka, T.; Oishi, T. Tetrahedron Lett. 1983, 26, 2653.

 ⁽a) Davis, F.A.; Chao, B.; Fang, T.; Szewczyk, J.M. Org. Lett. 2000, 2, 1041; (b) Mayer, M.; Thiericke, R. J. Org. Chem. 1993, 58, 3486; (c) Grabley, S.; Hammann, P.; Kluge, H.; Wink, J.; Kricke, P.; Zeeck, A. J. Antibiot. 1991, 44, 797.

The examples in Sections 6.2.D and 6.2.E show modifying the nature of the heteroatom (alcohol versus ether; amine versus amide versus sulfonamide versus azide) can control chelation effects, and the choice of reagent (changing the metal in metal hydrides for example). Such chelating effects have also been used extensively in cyclic systems, and those applications will be discussed in Sections 6.4 and 6.5.

6.3. STEREOCONTROL IN CYCLIC SYSTEMS

Many problems encountered in acyclic systems also arise in cyclic systems. The methods for controlling Markovnikov and anti-Markovnikov regiochemistry, as well as retention or inversion of the configuration are essentially the same as in acyclic systems. It is difficult to separate regiochemical (mode of addition) effects and retention versus inversion effects from cis-trans isomerism in cyclic molecules. Addition to a substituted π bond leads to geometrical isomers, and subsequent reactions give cis-trans isomers and/or diastereomers. The terms syn and anti have no meaning in cyclic systems, and only three discussions fundamental to cyclic molecules will be presented: control of diastereoselectivity, inversion of configuration of a stereogenic center, and the chelating effects of heteroatoms.

An important and differentiating feature of cyclic systems is the relatively rigid conformations assumed by these molecules (sec. 1.5.B). In both Chapters 3 and 4, conformational bias had a profound effect on reaction pathways, and also on the trajectory of attack. These effects provide the tools to control selectivity.

6.3.A. Regioselectivity

The problems associated with regioselective addition to cyclic molecules are essentially the same as those noted in acyclic molecules. Reaction of HBr with methylcyclopentene is highly regioselective for the Markovnikov product, tertiary bromide 1-bromo-1-methylcyclopentane. Methylcyclopentene, however, gave an 86:14 mixture of *trans*-2-methyl-2-cyclopentanol:1-methyl-1-cyclopentanol after hydroboration.²⁶ As with acyclic systems, regioselectivity improved as the steric bulk of the hydroboration reagent increased. Reaction with 9-BBN followed by oxidation gave an almost quantitative yield of *trans*-2-methyl-2-cyclopentanol.²⁷ As with acyclic molecules, understanding the mechanism associated with a given transformation is essential for controlling regioselectivity.

For E2 (anti) elimination (sec. 2.9.A) and syn elimination (sec. 2.9.C) reactions were discussed, regiocontrol in the elimination was achieved by allowing the base to attack the molecule in a bimolecular reaction (an external base for anti or E2 elimination) or by binding the base to the molecule (an internal base for syn elimination). Treatment of a halide such as **49** with potassium

^{26.} Zweifel, G.; Brown, H.C. Org. React. 1964, 13, 1.

^{27.} Brown, H.C. Organic Synthesis Via Boranes, Wiley, New York, 1973, p55.

tert-butoxide in *tert*-butanol led to anti elimination and formation of the more substituted alkene (**50**), which is due to the late transition state of the reaction (the Hammond postulate). Electronic requirements position the leaving group anti to the hydrogen being removed, and effectively lock the conformation of that transition state. The same effect is observed in cyclic halides such as *cis*-2-bromo-1-methylcyclopentane (**51**), which gives methylcyclopentene (**52**) upon treatment with base. The major difference, of course, is the inability of the ring to rotate about the carbon-carbon bonds. Nonetheless, the more highly substituted (more stable) alkene is also produced. For both syn and anti elimination, the β -hydrogen and the leaving group are fixed by the regiochemistry of the halide. *syn*-Elimination involves intramolecular attack of base, dictating removal of the β -hydrogen that is syn to the leaving group. The steric demands of this syn transition state make approach and removal of the less substituted β -hydrogen energetically more favorable. Conversion of **53** to sulfoxide **54** gives the less substituted alkene (3-methyl-1-cyclopentene, **55**) upon thermolysis.



Alkene positional isomerism is occasionally a problem, and it is conceptually related to regiochemistry. Careful choice of synthetic route and reagents is usually required to solve this problem, as illustrated by the Burk and Soffer synthesis of ε -cadinene (57) and γ_2 -cadinene (58).²⁸ Conversion to the ketone by hydrolysis of the vinyl ether unit in 56 was followed by conversion to the tertiary alcohol by reaction with methyllithium (sec. 8.5.C). When the alcohol was converted to the tertiary chloride, elimination with thionyl chloride/pyridine gave 57. Conversely, hydrolysis of the vinyl ether unit in 56 to a ketone followed by Wittig olefination (sec. 8.8.A) of the ketone gave the exo methylene derivative, 58. It is important to note that formation of the C2-C3 C=C unit over the C3-C4 unit in 57, by elimination of the tertiary chloride precursor is favored for trans decalin derivatives such as this.



^{28.} Burk, L.A.; Soffer, M.D. Tetrahedron 1976, 32, 2083.

6.3.B. Bredt's Rule

As we have just seen in the formation of **57** or **58**, regioselectivity is important for the formation of double bonds in elimination reactions. A unique regiochemical problem arises in small bicyclic compounds. Elimination of the bromine and H in 2-bromonorbornane (**59**) gave exclusively the Δ^2 -norbornene (**60**) and none of the Δ^1 -norbornene (**61**). Formation of an alkene such as **61** requires that bridgehead carbon atoms be compressed toward planarity, but the π overlap required for a planar C=C unit would be diminished due to structure-imposed twisting. The transition state energy required for elimination to a bridgehead carbon in small systems is typically very high, and small bicyclic systems *cannot* accommodate this great increase in strain. The observation that carbon-carbon double bonds cannot be formed to bridgehead atoms in small bicyclic rings is formally called **Bredt's rule**.²⁹ As originally stated by Bredt, "in systems of the camphane (**62**) and pinane (**63**) series and related compounds, the bridgehead carbons (*a* and *b*) cannot be involved in a carbon double bond."^{29a,b} As a corollary, reactions that should lead to such compounds will be hindered or will take a different course.²⁹ It has been noted that small bridgehead systems that tolerate a trans double bond will violate Bredt's rule.^{30,29}



How large must ring systems be before Bredt's rule does not apply? For [2.2.1], [2.1.1], and [1.1.1] bicyclic systems, Bredt's rule is applied. Prelog and co-workers established that cyclization of **64** gave **65** when n > 6.^{31,29} When n = 5, both **65** and **66** were formed, but **65** was not formed when n < 5.



^{29. (}a) Bredt, J.; Houben, J.; Levy, P. *Berichte* **1902**, *35*, 1286; (b) Bredt, J. *Annalen* **1924**, *437*, 1; (c) Fawcett, F.S. *Chem. Rev.* **1950**, *47*, 219; (d) Köbrich, G. *Angew. Chem. Int. Ed.* **1973**, *12*, 464.

 ⁽a) Weiseman, J.R.; Chong, J.A. *Ibid.* 1969, 91, 7775; (b) Wiseman, J.R.; Pletcher, W.A. *Ibid.* 1970, 92, 956;
 (c) Quinn, C.B.; Wiseman, J.R. *Ibid.* 1973, 95, 1342, 6120; (d) Quinn, C.B.; Wiseman, J.R.; Calabrese, J.C. *Ibid.* 1973, 95, 6121; (e) Krabbenhoft, H.O.; Wiseman, J.R.; Quinn, C.B. *Ibid.* 1974, 96, 258; (f) Marshall, J.A.; Fauble, H. *Ibid.* 1970, 92, 948.

 ⁽a) Prelog, V.; Ruzicka, L.; Barman, P.; Frenkiel, L. *Helv. Chim. Acta* 1948, 31, 92; (b) Prelog, V.; Barman, P.; Zimmermann, M. *Ibid.* 1949, 32, 1284; (c) Prelog, V. J. Chem. Soc. 1950, 420.

Fawcett attempted to correlate the lower limit of Bredt's rule by calculating the sum of the numbers of the bridged atoms [m + n + o = S] in systems such as **63** and **63** with three bridges.^{29c} For **62**, S = 2 + 2 + 1 = 5, and for **63**, S = 3 + 1 + 1 = 5. In Prelog's example (**64**), this [6.3.1] system has S = 9 when n = 5, and Bredt's rule does not apply. When the values of n are < 5, however, Bredt's rule applies for **64**. Relatively small bridgehead alkenes with a [3.3.1] system such as **67** (S = 7) can be prepared by pyrolysis of β -lactone **68** or ammonium salt **69**.³² Figure 6.1^{29d} shows several small bicyclic ring systems for S = 2 to S = 7, and analysis of these alkenes suggests that the constraints upon Bredt alkenes are important when S is 7 or less.



Figure 6.1. Typical Bredt alkenes. [Reproduced with permission from Köbrich, G. *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 464. Copyright 1973 VCH Weinheim.]

Köbrich established three guidelines^{29d} that govern the application of Bredt's rule.

- 1. For homologs with different S values, the ring strain varies inversely with S.
- 2. For a given *S*, the ring strain varies inversely with the size of the larger of the two rings with respect to which bridgehead bond is endocyclic.

^{32. (}a) Marshall, J.A.; Faubl, H. J. Am. Chem. Soc. 1967, 89, 5965; (b) Chong, J.A.; Wiseman, J.R. Ibid. 1972, 94, 8627 and references cited therein.

3. For a given bicyclic ring skeleton, the ring strain varies inversely with the size of the bridge containing the bridgehead double bond.

For example, these rules predict that **70** is more stable than **71**.³³ These three rules do not allow direct comparison in every case, but are generally applicable. Köbrich presented a list of carbocyclic Bredt's compounds^{29d} and stated that many heteroatom and polycyclic analogs can be included in the Figure 6.1 list.^{29d}



6.3.C. DIASTEREOSELECTIVITY

As mentioned previously, reactions of cyclic molecules that involve formation of stereogenic centers are similar to those of acyclic systems in that they can proceed with clean retention or inversion of configuration, or a mixture of the two. Reaction of sodium azide (NaN₃) and *cis*-4-*tert*-butyl-1-bromocyclohexane is expected to give *trans*-4-*tert*-butylazidocyclohexane with complete inversion of configuration via an $S_N 2$ pathway. In Section 1.5.B, we saw that many cyclic systems exist primarily in one or two low energy conformations, which can be used to control stereochemistry if other groups are present that sterically block approach of a reagent. A typical example is the reduction of a ketone moiety in a cyclic or polycyclic substrate, where the diastereoselectivity of the reduction is controlled by the conformational constraints of the system. In a synthesis of malayamycin A³⁴ by Hanessian and co-worker's, the ketone unit in **72** was reduced to the alcohol unit in **73** with high diastereoselectivity. The conformation of the ring allowed the diastereoselective reduction to proceed with sodium borohydride, rather than requiring one of the more expensive hydride reducing agents.



In many cases, reaction conditions and strategy combine to give a product with the incorrect stereochemistry at a key center, often an alcohol. In **74**, an intermediate in Philips and Chamberlin's synthesis of dysiherbaine,³⁵ the stereochemistry of the secondary alcohol is incorrect for the synthetic target. In order to invert the stereochemistry, **74** was oxidized with TPAP and NMO (see Section 3.2.F.i.) to give a 95% yield of ketone **75**. Subsequent reduction with NaBH₄ gave a quantitative yield of **76** with the correct stereochemistry. The observed inversion is possible because approach of the hydride reagent to the carbonyl unit in **76** is

^{33.} Wiseman, J.R.; Chan, H.-F.; Ahola, C.J. J. Am. Chem. Soc. 1969, 91, 2812.

^{34.} Hanessian, S.; Marcotte, S.; Machaalani, R.; Huang, G. Org. Lett. 2003, 5, 4277.

^{35.} Phillips, D.; Chamberlin, A.R. J. Org. Chem. 2002, 67, 3194.

restricted by the presence of the tricyclic system and other substituents, as well as the requisite Bürgi-Dunitz trajectory common to hydride reduction of ketone units (see Sections 4.7.C and 6.6.A). Oxidation followed by reduction of a carbonyl is a simple, yet powerful tool for modifying stereochemistry.



Sometimes, the natural selectivity of a reaction leads to a product with the incorrect stereochemistry required for a given target, but it may be possible to change it. There are at least two options: (1) change the stereocenter in the final product., as in $74 \rightarrow 76$, or (2) change the synthetic pathway to generate a compatible intermediate that can produce the desired stereochemistry.

One type of stereocenter that can be corrected is a CHX moiety, where X is an electronwithdrawing group and the H can be removed by treatment with base to form a planar enolate anion (secs. 9.1, 9.2). In a synthesis of quinine and quinidine by Jacobsen and co-workers,³⁶ lactam 77 (as a 1:1.7 mixture of *cis:trans* isomers) was converted to the enolate anion 78A with lithium diisopropyl amide (sec. 9.2). Inspection of a model of the enolate anion (78B) suggests that protonation will occur from the less hindered top face (A), rather than from face B. The model also suggests that there is only a small difference in steric hindrance of one face relative to the other, and this observation is consistent with the isolated product, a 3:1 mixture favoring 79. Exploiting such differences in product stability allows one to change the diastereomer population.



The second approach noted above for correcting stereochemistry is illustrated by formation of epoxides **82** and **84** from conjugated ketone **80**, by Grieco and co-workers.³⁷ Epoxidation of **80**

^{36.} Raheem, I.T.; Goodman, S.N.; Jacobsen, E.N. J. Am. Chem. Soc. 2004, 126, 706.

 ⁽a) Grieco, P.A.; Ohfune, Y.; Majetich, G. J. Org. Chem. 1979, 44, 3092; (b) Ohfune, Y.; Grieco, P.A.; Wang, C.-L.J.; Majetich, G. J. Am. Chem. Soc. 1978, 100, 5946.

from the less hindered α face gave **81**, and reduction from that same face gave **82**. The relative stereochemistry was different, however, when initial reduction of **80** (hydride was delivered from the β -face) gave alcohol **83**. Subsequent epoxidation proceeded via coordination of the OH unit in **83** with the epoxidation agent (MCPBA, sec. 3.4.C), and the final product was **84** with the epoxide and hydroxyl unit cis (syn) to each other.³⁷ Simply changing the order of reactions allowed Grieco to target one diastereomer or the other.



One major difference between cyclic and acyclic systems is the inability of cyclic systems to undergo rotation about carbon-carbon bonds, leading to relatively well-defined conformations. If *trans*-4-*tert*-butyl-1-bromo-cyclohexane is used as an example, there is the usual equilibrating population of the two chair conformations (sec. 1.5.D). The diequatorial conformer is significantly more stable and accounts for the major portion of the equilibrium (sec. 1.5.B). According to Corey's calculations³⁸ from Section 1.5.D, the equatorial form predominates (>99.99:<1, diequatorial/diaxial). Molecular modeling indicates that the diequatorial conformation is nearly 32 kJ mol⁻¹ lower in energy than the diaxial conformation, with a Boltzmann distribution favoring more than 99.99% of the diequatorial conformation. To predict the major product, nucleophilic backside attack on both conformations must be considered, and the less sterically hindered pathway is usually preferred. In this case, the diequatorial conformation is more reactive.

In a conformationally anchored system such as **85**, $S_N 2$ displacement of the equatorial bromine may be extremely slow. If the reaction is too slow, the temperature can be raised and a more polar solvent (DMF, DMSO, etc.) can be used (secs. 2.7.A, 2.6.Ai). In some cases, the more vigorous reaction



conditions will lead to an alternative reaction (such as elimination or thermal decomposition) rather than the desired $S_N 2$ displacement. Similarly, dibromide **86** is expected to undergo nucleophilic substitution in ring B since displacement of the bromide in ring A is very slow.

^{38.} Corey, E.J.; Feiner, N.F. J. Org. Chem. 1980, 45, 765.

The relative stereochemistry of the leaving group is very important for intramolecular reactions, as seen in Corey and Watt's synthesis of α -copaene and α -ylangene.³⁹ Displacement of the tosyl group in **87** by the nucleophilic carbon of the enolate anion (**88A**, formed with dimsyl sodium, sec. 9.2.A and 9.3.A) gave the bridged product (**89**) characteristic of the ylangene natural products. Examination of the conformational drawing for **87** (see **88B**) reveals that the enolate carbon is properly oriented to attack the tosyl carbon from the rear, so displacement of the OTs group is possible only when it is in the equatorial position and is syn to the bridgehead methyl group. Note the letters marking the key atoms. The isomeric axial tosylate (**90**; the tosyl group is anti to the bridgehead methyl group) cannot be displaced via backside attack, since the enolate carbon cannot approach the tosyl carbon from the rear. Ketone **87** will react as shown to give **89**, but the isomeric ketone **90** will not.



Marshall et al. showed that alkenyl aldehydes can be cyclized on acidic silica gel, and the stereochemistry of the bicyclic alcohol product is controlled by the cis or trans geometry of the monocyclic precursor.⁴⁰ This reaction is an **ene reaction** (sec. 11.13), which is particularly effective when catalyzed by Lewis acids.^{40c,d} The cis precursor **91** was cyclized to **92**, whereas the trans aldehyde **93** was cyclized to **94**. Formation of a seven membered ring in **92** requires a seven-membered chair-like ring for the ene reaction to occur (see **95**). If the oxygen is in the axial position (see **96**) rather than the equatorial position (see **95**), then the alkenyl group is further removed from the acylium cationic center, and transfer of the hydrogen and attack by the π bond for an ene reaction is more difficult. Cyclization of **93** requires transition state **98**. This transition for efficient hydrogen transfer and attack by the alkene, leading to **94**. The opposite conformation with the equatorial oxygen (see **97**) has a greater transannular steric interaction, and is also in a higher energy boat-like transition state that disfavors the ene reaction in this particular system.



^{39.} Corey, E.J.; Watt, D.S. J. Am. Chem. Soc. 1973, 95, 2303.

^{40. (}a) Marshall, J.A.; Andersen, N.H.; Johnson, P.C. J. Org. Chem. 1970, 35, 186; (b) Marshall, J.A.; Andersen, N.H.; Schlicher, J.W. Ibid. 1970, 35, 858; (c) Snider, B.B. Acc. Chem. Res. 1980, 13, 426.



When an alkene unit is the product of a reaction, there is the potential for both (E) and (Z)isomers. The examples previously cited for E2 and syn elimination are illustrative. In both cases, the stereochemistry (E) or (Z) of the double bond is important. Stereochemistry may be controlled in acyclic systems by using resolved chiral precursors because the E2 elimination is stereospecific. Controlling cis-trans isomers for alkene derivatives is also possible in medium and large ring molecules, and other reactions are known that introduce the C=C unit. Corey and co-worker's synthesis of caryophyllene (102) and isocaryophyllene (106) illustrates this type of control.⁴¹ A Grob fragmentation⁴² (sec. 2.9.E) in 99 led to the (Z)-double bond in 100, required for **102**. The geometry of the double bond was controlled by changing the stereochemistry of the carbon bearing the leaving group in the cyclic precursor (see a discussion of this technique in sec. 6.5). Once the (Z)-double bond had been incorporated, the α -hydrogen was equilibrated (via enolization with potassium *tert*-butoxide) from the initially formed cis ring juncture (in 100) to the more stable trans-ring juncture in 101. To obtain the other geometric isomer (in 106) the relative stereochemistry of the OTs group had to be changed to that shown in **103**. A Grob fragmentation of 103 gave the (E)-double bond in 104 that is characteristic of 106.⁴² As before, the cis-ring juncture in 104 was equilibrated to the more stable trans ring juncture in 105 by enolization prior to conversion to 106. These examples show that the (E/Z)-stereochemistry of the alkene products was established by the relative stereochemistry of the tosylate precursors, once the reaction to generate the double bond in those alkenes was chosen.



^{41. (}a) Corey, E.J.; Mitra, R.B.; Uda, H. J. Am. Chem. Soc. 1963, 85, 362; (b) Idem, Ibid. 1964, 86, 485.

^{42.} Grob, C.A. Angew. Chemie, Int. Ed. 1969, 8, 535.



6.4. NEIGHBORING GROUP EFFECTS AND CHELATION EFFECTS

The influence of heteroatom substituents to direct reactivity to one face or another has been noted in this as well as several preceding chapters. In Chapter 3, a neighboring group effect influenced delivery of oxygen to the double bond of an allylic alcohol, described by Henbest and by Sharpless (secs. 3.4.B, 3.4.C). The effect is identical to the effect described for acyclic control in Section 6.2.E (see above). Peroxyacid epoxidation of **107** proceeded via coordination of the peroxyacid to the alcohol (see **108**) to deliver the electrophilic oxygen from that face to give **109**.²² This result contrasts with epoxidation of allylic acetate **110**, which gave primarily **111**



via delivery from the less sterically hindered face. The acetate group inhibits coordination with the peroxyacid, and delivery of the electrophilic oxygen is from the less sterically hindered face, so the epoxide unit is on the opposite side of the ring. A synthetic example of this effect is taken from a synthesis of the A/B ring of ouabain by Jung and Piizzi,⁴³ in which epoxidation of allylic alcohol **112** occurred from the same face as the hydroxyl group via a neighboring group effect, to give a 96% yield of **113**. Note that this effect was seen in the conjugate epoxidation of ketone **80**, versus the alcohol-directed epoxidation of **83** (see above).³⁷ In zinc borohydride [Zn(BH₄)₂] reductions, oxygen atoms can chelate with the zinc.²⁴ In a synthesis of a C1-C22 fragment of leucascandrolide A, Panek and Dakin treated **114** with zinc borohydride. Coordination of the zinc reagent with the hydroxyl unit led to formation of **115** in 80% yield,

^{43.} Jung, M.E.; Piizzi, G. Org. Lett, 2003, 5, 137.

with a dr of >15:1 favoring the diastereomer shown.⁴⁴



Hydroboration of alkenes to give alcohols typically follows an anti-Markovnikov orientation (sec. 5.2.A). Chelation effects can sometimes control the product distribution, but the mere presence of a heteroatom does not always mean that this will be the case. Hydroboration of **116** (tabersonine) is an example where the hydroboration-oxidation sequence (sec. 5.4.A) gave **117** in



90% yield, as a mixture of diastereomeric secondary alcohols (4:1 β/α mixture favoring **117**). This reaction was part of the Caron-Sigaut et al. synthesis of 14-hydroxyvincadifformine,⁴⁵ but they showed that chelation was *not* an important factor contrary to what might

be suspected from a cursory examination of the starting materials. The enamine unit in **116** is part of a bicyclic system where the exo face is more accessible, leading to the stereochemistry in **117** (secs. 1.5.E, sec. 4.7.E). The regiochemistry of the alcohol unit in **117** probably results from steric interactions as borane approaches the C=C unit. Brown showed that electronic and chelation effects can be important in the hydroboration of allylic amines (sec. 5.2.A.iv), but in **116** steric factors control the reaction.

Chelation is important in the dihydroxylation of **118** with osmium tetroxide (sec. 3.5.B), and reduction of the intermediate iminium ion gave **119**, in a synthesis of $\Delta^{20'}$ -20'-deoxyvinblastine.^{46b} This transformation is compared with the reaction of **118**^{46a} with thallium acetate, where reduction of the intermediate iminium ion gave the epimeric alcohol **120**. The nitrogen lone pair



^{44.} Dakin, L.A.; Panek, J.S. Org. Lett. 2003, 5, 3995.

^{45.} Caron-Sigaut, C.; Le Men-Olivier, L.; Hugel, G.; Lévy, J.; Le Men, J. Tetrahedron 1979, 35, 957.

 ⁽a) Mangeney, P.; Andriamialisoa, R.Z.; Langlois, N.; Langlois, Y.; Potier, P. J. Am. Chem. Soc. 1979, 101, 2243; (b) Langlois, N.; Potier, P. Tetrahedron Lett. 1976, 1099.

is responsible for the reversal of diastereoselectivity. Osmium tetroxide (OsO₄) does *not* coordinate well to the nitrogen and the osmate ester is formed on the less hindered α face of **121**, which leads to diol **122**. Elimination of the α -hydroxylamine gave an iminium salt (**123**) that was subsequently reduced with NaBH₄ to give **124** (product **119** above). Thallium (III), however, coordinates quite well to the nitrogen lone pair (as in **125**) to give **126**. Transfer of an oxygen from one acetate unit to the enamine moiety (secs. 9.6.A,B), from the β face, gives **127**. Reduction leads to **128** (product **120** above).



Neighboring group effects usually influence stereo- and regiochemistry of the functional group close to the chelating atom or group. Such effects that can influence a reaction at sites distant from the coordination point.⁴⁷ An example of a neighboring group effect with consequences at a remote site is the photochemical isomerization of **129** (n = 1) to **130**, in 55% yield (sec. 13.5.E for a brief discussion of this concept).⁴⁸ The β -C3 hydroxyl group was converted to an ester, and the benzophenone moiety was positioned on the β face of the molecule by a chain of methylene units. Irradiation generated the benzophenone triplet (see secs. 13.4, 11.10.B for a brief introduction to photochemical techniques), and with an appropriate methylene spacer [(CH₂)_n] the hydrogen at C14 was selectively removed to give the $\Delta^{14\cdot15}$ alkene (**130**, n = 1). With this

particular spacer, the C8 hydrogen on the α face of the molecule is inaccessible and not removed. Longer or shorter methylene spacers (n = 0, n > 2) led to a diminished yield of **130**.



^{47.} For examples, see (a) Sailes, H.; Whiting, A. J. Chem. Soc. Perkin Trans. 1 2000, 1785; (b) Mitchell, H.J.; Nelson, A.; Warren, S. J. Chem. Soc. Perkin Trans. 1 1999, 1899.

^{48.} Breslow, R. Chem. Soc. Rev. 1972, 1, 553.

Neighboring group effects can compete with steric effects, as illustrated by treatment of oxetane **131** with diethylaluminum-*N*-methylaniline. This elimination reaction gave a 99% yield of (*E*)-alkene **132** in a synthesis of humulene.⁴⁹ The aluminum coordinated to the oxetane oxygen on the less hindered β face in **133** and **134**, the two key rotamers. Rotamer **133** is lower in energy due to the severe non-bonded interaction of the propyl group, and the oxetane methyl in **134**. Removal of the indicated hydrogen by the basic nitrogen, in a six-center transition state as seen in **133**, led to the (*E*) isomer **132**. Removal of hydrogen in **134** would give the (*Z*) isomer, but the relatively high energy of that species relative to **133** makes it disfavored.



In planning a reaction, not only the obvious effects of α or β hydroxyl, alkoxy or amino groups must be considered, but also the more subtle effects of nearby heteroatom lone pairs. These chelating effects are apparent both in directing stereochemistry or regiochemistry and in slowing or stopping a desired reaction. These effects can be used synthetically to direct attack of a reagent, as shown above. If one wishes to prevent the chelating effect, the offending group must be blocked or removed. Alternatively, the planned synthetic sequence can be accomplished before the chelating atom is present. Careful analysis of all synthetic intermediates is required to use or avoid these effects.

6.5. ACYCLIC STEREOCONTROL VIA CYCLIC PRECURSORS

It is apparent from preceding sections that stereocontrol in cyclic systems is much easier than in acyclic systems, which is due of course, to the conformational bias inherent in cyclic systems. Synthetic chemists have exploited this fact for many years. A cyclic system can be used to position functional groups, often with control of regio- and stereochemistry. The ring is then opened to give an acyclic system. and the regio- and stereochemistry of the substituents has been fixed. There are many examples.

In Chapter 3, ozonolysis (sec. 3.7.B) of cyclic alkenes was shown to generate α,ω -functionalized systems. The utility of the process is demonstrated by the ozonolysis of 1,5-cyclooctadiene to give diol **135** in 85% yield.⁵⁰ Conversion of **135** to the racemic sex pheromone of the female

^{49.} Kitagawa, Y.; Itoh, A.; Hashimoto, S.; Yamamoto, H.; Nozaki, H. J. Am. Chem. Soc. 1977, 99, 3864.

 ⁽a) Tolstikov, G.A.; Odinokov, V.N.; Galeeva, P.J.; Bekeeva, R.S. *Tetrahedron Lett.* 1978, 1857; (b) Tolstikov, G.A.; Odinokov, V.N.; Galeeva, R.I.; Bakeeva, R.S.; Rafikov, S.R. *Dokl. Akad. Nauk, SSSR* 1978, 239, 1377 (Engl., p. 174).

face fly (136) required four steps.⁵⁶ Examining the overall sequence shows that the α -and ω -functional groups were incorporated by sequential alkylation reactions at the hydroxyl groups in 135. Functionalization of each hydroxyl unit and then the alkene unit gave 137.



The synthesis of (–)-(R)-muscone by Fehr and co-workers⁵¹ is another example of inserting and positioning functional groups, involving the conversion of **137** to **139**. Treatment of ketone **137** with tosylhydrazine gave an 87% yield of hydrazone **138**. Subsequent reaction with an excess of peroxyacetic acid generated the epoxy-hydrazone *in situ*, and subsequent fragmentation by what is known as **Eschenmoser ring cleavage**⁵² gave keto-alkyne **139**. This named reaction transforms an epoxy-ketone to a keto-alkyne.



The diastereoselectivity obtained for reactions on a ring makes it possible to use a cyclic molecule to fix a stereocenter in an acyclic target, as seen in the formation of **142** from **140**. In a synthesis of ceramides, Hung and co-workers converted D-Glucosamine **140** to the azide **141** by a four-step sequence, with control of the stereocenters.⁵³ Further elaboration of the functionality in 7 steps led to ring opening to produce amino-tetraol **142** where the relative stereochemistry of this fragment was fixed by manipulation of the cyclic precursors.



6.6. **RING-FORMING REACTIONS**

6.6.A. Baldwin's Rules

Cyclic compounds play an important role in organic synthesis. The desired compound is not always commercially available, however, and must often be prepared by cyclization reactions

^{51.} Fehr, C.; Galindo, J.; Etter, O. Eur. J. Org. Chem. 2004, 1953.

^{52.} Müller, R.K.; Felix, D.; Schreiber, J.; Eschenmoser, A. Helv. Chim. Acta 1970, 53, 1479.

^{53.} Luo, S.-Y.; Kulkarni, S.S.; Chou, C.-H.; Liao, W.M.; Hung, S.-C. J. Org. Chem. 2006, 71, 1226.

from acyclic precursors. This is particularly true for large ring (macrocyclic) compounds and polycyclic molecules. In the latter case, a cyclic molecule acts as a template and the other rings are built onto the template (this is called **annulation**). This section will discuss the salient features of ring-forming reactions commonly encountered in synthesis.

An introduction to cyclization reactions is best begun with a discussion of **Baldwins rules for ring closure**, or simply **Baldwin's rules**. Baldwin studied many nucleophilic, homolytic or cationic ring-closing processes and found a predictable pattern of reactivity. This approach is based on the stereochemical requirements of both reagent and substrate as well as the angles of approach that are allowable when two reactive centers come together.

To form a ring, the two reactive centers are connected by a tether of atoms (usually carbon atoms but not always, and this restriction imposes constraints on the angles from which the reactive centers can approach one another, and on the stereochemistry of the product. If the length and nature of the chain (tether) linking terminal atoms X and Y allows this geometry to be attained, ring formation is possible (**favored**), and we make the predication that the reaction will succeed. If the proper geometry cannot be attained, ring formation is difficult (**disfavored**) and competitive processes often dominate. Baldwin classified ring closing reactions into two categories: **exo** (the electron flow of the reaction is external to the ring being formed [**144** from **143**], and **endo** [the electron flow is within the ring being formed (**146** from **145**)].⁵⁴ Baldwin further classified reactions according to the hybridization of the atoms accepting the atom in the ring closing process. If the atom being attacked is sp³ hybridized, as in **147**, the reaction is termed **tet**, and an exo-tet reaction will generate a ring such as **148**. Attack at an sp² atom (**143**) is termed **trig** (forming the ring **144** or **146**). Attack at an sp hybridized atom (**149**) is **dig**, and an exo-dig reaction will generate ring **150**.



It is therefore possible to describe ring forming reactions by the number of atoms in the cyclic product, whether the reaction is exo or endo, and whether it involves **tet**, **trig**, or **dig** intermediates. A **5-exo-tet** reaction represents formation of a five-membered ring by displacement at sp³ carbon by X, where Y is exo to the ring being formed. The cyclization reactions that form 3-7 membered rings, along with all **exo/endo**, and **tet/trig/dig** possibilities are shown in Figure 6.2.⁵⁴

^{54. (}a) Baldwin, J.E. *J. Chem. Soc. Chem. Commun.* **1976**, 734; (b) Baldwin, J.E.; Cutting, J.; Dupont, W. Kruse, L.; Silberman, L.; Thomas, R.C. *Ibid.* **1976**, 736.



Figure 6.2. Ring closures categorized by Baldwin's rules.

When two reactive ends of a molecule come together, they can approach each other only from certain trajectories called the angle of attack. Before discussing Baldwin's rules, it is first necessary to establish what angles of attack are most likely. Elliot and Graham-Richards described a method for predicting the preferred approach angles based only on the substrate.⁵⁵ Note that these models assume a late transition state, so that the

bond angles in the product are close to those in the important transition state (the Hammond postulate). Displacement at a sp³ carbon generally requires backside attack (see **151**) and the incoming group (**X**) must approach the **Y**-bearing carbon at an angle close to 180° . For exo processes, this is usually easy but for endo processes it can be difficult. Reactions at double bonds (trig) are controlled by the planar nature of alkenes, imines or carbonyls. The bond angles are about 120° , but upon reaction the sp² atom is converted to a sp³ atom. Since sp³ atoms are tetrahedral (with bond angles of about 109° , sec. 4.7.C), the best trajectory for attack of a sp² atom (a carbonyl, for example) is about 109° (the Bürgi-Dunitz trajectory;⁵⁶ see **152**).

$$\mathbf{X}^{-} \xrightarrow{\alpha} \mathbf{Y} \xrightarrow{\alpha = 180^{\circ}} \mathbf{X} \xrightarrow{\alpha} \mathbf{Y}^{-} \xrightarrow{\mathbf{X}^{-}} \mathbf{Y}^{-} \xrightarrow{\mathbf{X}^{-}} \mathbf{Y} \xrightarrow{\alpha = 109^{\circ}} \mathbf{Y} \xrightarrow{\mathbf{X}^{-}} \mathbf{Y}^{-}$$

Treatment of 153 with azobis (isobutyronitrile), AIBN, and tributyltin hydride leads to a radical

^{55.} Elliot, R.J.; Graham-Richards, W. J. Mol. Struct. 1982, 87, 247.

^{56.} Bürgi, H.B.; Dunitz, J.D.; Lehn, J.M.; Wipff, G. Tetrahedron 1974, 30, 1563.

intermediate (154)⁵⁷ (see sec. 13.7 for a discussion of radical cyclization). Attack at the alkene unit easily allows approach at 109°, and cyclization gives 155. Hydrogen transfer to 155 from Bu_3SnH completes the reaction, and generates the product 156. Formation of large rings is not a problem with respect to Baldwin's rules, because there is sufficient flexibility in the tether to attain the required approach angle.⁵⁸



Molecules containing a triple bond have a linear geometry, so the bond angles are 180°. Conversion of the sp atom to an sp² atom with the 120° bond angle characteristic of alkenes. Using the same analogy as for the sp²-sp³ conversion, an incoming atom should approach the triple bond at an angle of $\approx 120^{\circ}$ (see 157).⁵⁹ Ring closure is difficult for reactions where the chain is small (*a* in 158). With longer chains (*b* and *c* in 158) the process may be more facile. For intramolecular reactions, attack at an angle of 120° or greater is possible in most cases (see 159).



These observations led Baldwin to establish several rules for ring closure, known as **Baldwin's** rules:⁵⁴

- 1. For tet systems: 3-7 exo-tet are *favored* 5-6 endo-tet are *disfavored*
- 2. For trig systems: 3-7 exo-trig are *favored* 6-7 endo-trig are *favored* 3-5 endo-trig are *disfavored*
- **3.** For dig systems: **5-7 exo-dig** are *favored* **3-7 endo-dig** are *favored* **3-4 exo-dig** are *disfavored*

The disfavored reactions are not impossible, simply more difficult and usually slower than other competing reactions (inter- or intramolecular). Although some of the reactions show here will not be presented until Chapters 8, 9, 12 and 13, several examples of carbon-carbon bond forming reactions will be given to illustrate these rules.

When 160 reacted with KOH in aqueous acetonitrile, the 5-exo-trig product (161) was favored

 ⁽a) Padwa, A.; Nimmesgern, H.; Wong, G.S.K. J. Org. Chem. 1985, 50, 5620; (b) Idem Tetrahedron Lett. 1985, 26, 957; (c) Padwa, A.; Dent, W.; Nimmesgern, H.; Venkatramanan, M.K.; Wong, G.S.K. Chem. Ber. 1986, 119, 813; (d) Watanabe, Y.; Ueno, Y.; Tanaka, C.; Okawara, M.; Endo, T. Tetrahedron Lett. 1987, 28, 3953.

 ⁽a) Porter, N.A.; Magnin, D.R.; Wright, B.T. J. Am. Chem. Soc. 1986, 108, 2787; (b) Porter, N.A.; Chang, V.H.-T. Ibid. 1987, 109, 4976.

^{59.} Baughman, R.H. J. Appl. Phys. 1972, 43, 4362.

over formation of the 6-endo-trig product (162), by a ratio of $18:1.^{60}$ The alkynyl derivative (163) reacted 10^3 times slower than 160 and gave *only* the 5-exo-dig product (164). The 6-endodig product (165) was *not* isolated from the reaction, although the actual product distribution was probably > 100:1 favoring 164 over 165. It was suggested that sp atoms generally prefer the exo mode of attack to the endo mode.⁶⁰



There are reactions that seemingly contradict Baldwin's rules. Presumably, these are reactions with an early transition state that will have different angles of attack. Fountain and Gerhardt showed that *N*-methyl-*O*-cinnamoyl hydroxylamine gave 5-phenyl-3-pyrazolidinone (**166**, which exists as the two valence tautomers shown) under forcing conditions (15 h in refluxing dichlorobenzene), via the disfavored 5-endo-trig pathway.⁶¹ This simply illustrates that the rules say favored or disfavored, not allowed or forbidden. It does point out, however, that factors other than geometry and stereochemistry must be considered. Fountain suggested that electronic factors must be considered.⁶² Anselme showed that cyclization of **167** to **168** occurred via a 5-endo-trig process,⁶¹ but under more vigorous conditions than noted by Fountain for the cyclization of **165**. Presumably, the nitrogen lone pair electrons in **167** are more nucleophilic than in CO_2NHMe precursor to **166**.⁶²



- 60. Evans, C.M.; Kirby, A.J. J. Chem. Soc. Perkin 2 1984, 1269.
- 61. Fountain, K.R.; Gerhardt, G. Tetrahedron Lett. 1978, 3985.
- 62. Anselme, J.P. Tetrahedron Lett. 1977, 3615.

Epoxides and other three-membered rings present special problems since they are in between tet and trig systems. Generally, three membered rings prefer the exo mode of attack (see **169**) to give **170**.⁶³ The endo mode of attack generates **171**. If we use **172** as an example, protonation of the epoxide oxygen with an acid (camphorsulfonic acid) followed by attack by the OH unit and ring opening gave the observed products.⁶⁴ When R was CH₂CH₂CO₂Me, the 5-exo product **174** was the only one (94% yield), which is typical. When the R substituent in **172** was changed from alkyl to alkenyl (vinyl), however, the course of ring opening was changed to give only the 6-exo product (**173**) in 90% yield. In general, the 5-exo mode of attack is preferred.



Three-membered rings other than an oxirane ring follow the same ring opening pathways. An example of such an opening is the iodolactonization reaction discussed in Section 2.10.C. A synthetic example is taken from Imanishi and co-worker's synthesis of leustroducsin B, in which alkene-acid 175 was treated with bicarbonate in the presence of iodine and KI, to give carboxylate anion-iodonium intermediate $176.^{65a}$ Intramolecular displacement of iodide by carboxylate (**path** *a*) is a 5-exo process, and is favored over the analogous 6-endo process (**path** *b*) to give iodolactone 177 in greater than 80% yield. Note that this reaction may not proceed by the discrete iodination addition product 176, in which case Baldwin's rules do not apply.



^{63.} Stork, G.; Cohen, J.F. J. Am. Chem. Soc. 1974, 96, 5270.

^{64.} Nicolaou, K.C.; Duggan, M.E.; Hwang, C.-K.; Somers, P.K. J. Chem. Soc, Chem. Commun. 1985, 1359.

 ⁽a) Miyashita, M.; Tsunemi, T.; Hosokawa, T.; Ikejiri, M. Imanishi, T. *Tetrahedron Lett.* 2007, 48, 3829. For iodolactonization, see (b) Klein, J. J. Am. Chem. Soc. 1959, 81, 3611; (c) van Tamelen, E.E.; Shamma, M. *Ibid.* 1954, 76, 2315.

MOLECULAR MODELING: Intramolecular S_N2 Reaction

Ring closure of A can proceed via a 7-*endo* tet process to give **B**, or via a 6 *exo*-tet process to give pyran **C**. According to Baldwin's rules, **C** should predominate [see Janda, *et. al., J. Am. Chem. Soc.* **1995**, 117, 2659].



Is the six-membered ring also the thermodynamic product (both prior to and following protonation)? To decide, obtain energies for both pairs of compounds. Place each molecule in what you think is a favorable conformation but be careful to use the correct stereochemistry. Following the first calculation, *click* on > at the right of the tab at the top of the screen and select **Continue**. This will bring up a fresh builder palette without removing the text. Does your analysis allow you to conclude that the ring closure is under kinetic or thermodynamic control? Elaborate. Also see homework problem 4.

Third-row elements are difficult to analyze by Baldwin's rules because the atomic radii are larger and the bond lengths are large. Conformations can be attained that are unavailable to molecules that contain only second-row atoms. The constraints on approach angles are therefore less stringent. Thiol **178**, for example, was cyclized to **179** by a 5-endo-trig process (an internal Michael addition).^{54b,66} The sulfur atom has 3d orbitals and can receive electrons via back donation from the occupied p orbitals (see **180**). This ability diminishes the requisite angle of attack from 109° to 90° or less, facilitating the endocyclic ring closure.



Baldwin's rules also apply to ketone enolate anions,⁶⁷ but Baldwin and Lusch⁶⁸ modified the rules to make the terminology more specific. The special angular requirements of enolate anions are shown for the exo-tet -process (**181**), and the exo-trig process (**182**). For these two ring-closing reactions, the p orbitals of the enolate anion must approach the reactive center at an angle of about 180° or 109°, respectively. The orientation of the orbital and not just the nucleophilic atom (C or O) must be considered for determining the correct angle of approach (sec. 9.2.B).

See (a) Claeson, G.; Jonsson, H.-G. Arkiv. Kemi 1967, 28, 167 [Chem. Abstr., 68: 87083e 1968]; (b) Idem Ibid. 1966, 26, 247 [Chem. Abstr. 66: 85334x 1967].

^{67.} Baldwin, J.E.; Kruse, L.I. J. Chem. Soc. Chem. Commun. 1977, 233.

^{68.} Baldwin, J.E.; Lusch, M.J. Tetrahedron 1982, 38, 2939.



There are two ways to view the ring closure. A kinetic enolate anion (less substituted, derived from removal of the most acidic proton, sec. 9.2.E) such as **183** will close via exo displacement of Y to give **184**. A thermodynamic enolate anion (more substituted, resulting from equilibration to the most stable enolate anion product, sec. 9.2.E) such as **185** also undergoes an exo displacement of Y, but gives **186**. Conversion of **183** to **184** was termed enolendo-exo-tet, and conversion of **185** to **186** was termed enolexo-exo-tet. Similarly, exo-trig reactions can be classified in this manner. The kinetic enolate anion (**187**) gives **188** in an enolendo-exo-trig process. Cyclization of the thermodynamic enolate anion (**189**) gives **190** via an enolexo-exo-trig reaction.



The rules are somewhat different for ring closure with enolates.

6-7	enolendo-exo-tet	favored	3-5	enolendo-exo-tet	<u>disfavored</u>
3-7	enolexo-exo-tet	favored	3-7	enolexo-exo-trig	favored
6-7	enolendo-exo-trig	favored	3-5	enolendo-exo-trig	<u>disfavored</u>

Two competing intramolecular cyclizations (see the aldol condensation, sec. 9.4.A.ii) are illustrated for triketone **191**.⁶⁸ In this case, only the favored 6-enolendo-exo-trig product (**192**) was obtained, and not the disfavored 5-enol-endo-exo-trig products (**193** and **194**). Enolate anions



generally show 5-exo-tet reactions at oxygen, and 6-enolendo-exo-tet reactions at carbon. In order to form a five-membered ring from **195**, the oxygen lone pair must be at the correct angle for displacement of bromine (the product is tetrahydrofuran **196**). Another view of **195A** shows the positioning of the orbitals that will allow displacement (see **195B**). In order to generate a six-membered ring, however, the orbitals of the enolate carbon in **197** must be at the correct angle for displacement (see **197B**) and the product will be **198**.



6.6.B. Macrocyclic Compounds

6.6.B.i. Macrocyclic Ring Closures. Baldwin's rules explain most of the cyclization reactions for small- and medium-sized rings encountered in previous chapters, and those that will be seen in succeeding chapters. An exception is the formation of large rings. Formation of carbocyclic rings will be discussed in later chapters in connection with the appropriate carbon-carbon bond-forming reactions. Macrolactonization, however, is a functional group exchange process, and large lactone rings are also an important feature of many natural products. This section will discuss the problems and solutions for macrocyclic cyclizations. The principles discussed here for preparing large ring lactones are applicable to most other macrocyclizations.

Illuminati and Mandolini described the ring-closing reactions of bifunctional chain molecules.⁶⁹ In the 1920s and 1930s Ruzicka et al.⁷⁰ and Ziegler et al.⁷¹ studied macrocyclic reactions. Formation of macrocyclic rings usually requires an intramolecular cyclization reaction

of a bifunctional molecule such as **199**, where cyclization gives the monocyclic product, **200**. In this model, X and Y are reactive functional groups that generate a new bond, represented by Z (which may contain X, Y, or both). An important reaction that competes



with cyclization is the intermolecular reaction where initial coupling generates the dimeric species **201**. Repeated intermolecular reactions give oligomers or polymers (**202**). Ruggli discovered that high substrate concentrations favor polymerization, while low concentrations favor cyclization.⁷² The rate of cyclization is a function of the structure of the open-chain precursor and that of the product-like transition state. The activation energy for ring closure

^{69.} Illuminati, G.; Mandolini, L. Acc. Chem. Res. 1981, 14, 95.

^{70.} Ruzicka, L.; Stoll, M.; Schinz, H. Helv. Chim. Acta 1926, 9, 249.

^{71.} Ziegler, K.; Eberle, H.; Ohlinger, H. Annalen 1933, 504, 94.

^{72. (}a) Ruggli, P. Annalen 1912, 392, 92; (b) Idem, Ibid. 1913, 399, 174; (c) Idem Ibid. 1916, 412, 1.

is largely determined by the strain energy of the final ring.⁷³ As shown in Sections 1.5.A, 1.5.D, strain energy is due to "(1) bond opposition forces due to imperfect staggering (**Pitzer** strain), (2) deformation of ring bond angles (Baeyer strain), and (3) transannular strain due to repulsive interactions between atoms across the ring when they are forced close to each other."^{69,74} As the chain length increases for a cyclization reaction, the probability of the chain termini approaching each other decreases ("negative ΔS^{\ddagger} due to less freedom of internal rotation around single bonds of the molecular backbone when the disordered, open-chain precursor is converted to the ring shaped transition state").⁶⁹ In general, the ring product is a good model of the transition state of cyclization (a ring-shaped transition state) for all but the shortest chains.⁷⁵ When large rings are formed that are free of strain, there is minimal strain energy in the transition states. In short chains, an advantage in terms of entropy is offset by an increase in enthalpy due to extremely large strain energies. Ziegler first used this principle of a ringshaped transition state to generate large membered rings by is known as the **high dilution** method.⁷⁶ Cyclization of 203 to 204, for example, was accomplished by slow addition (6.6 x 10⁻⁴ mol L⁻¹day⁻¹) of bromoacid to a solvent containing potassium carbonate (K_2CO_3) or hydroxide.⁷⁷ For n = 9, a 77% yield of 204 was obtained.⁷⁷ The main side product of this process was the dimeric ester 205.



Bromocarboxylate **203** can be cyclized to a lactone and this simple reaction will be used to illustrate cyclization processes in general. An intramolecular cyclization reaction of **203** (governed by k_{intra}) will generate the lactone (**204**), but an intermolecular reaction (k_{inter}) will give the dimeric ester (**205**).⁶⁹ The relative preference of a reaction is given by the effective molarity (**EM**) = k_{intra}/k_{inter} .⁷⁸ The EM is supposed to be the first-order rate constant for ring closure times the second order rate constant for reaction between chain ends (if they were not connected), but the EM for five and six-membered rings exceeds the real concentration.⁶⁹ Two parameters similar to the EM are useful for predicting conditions under which a ring can be synthesized, free of significant polymerized byproducts.⁷⁹ The first is the parameter C α/M_o (see Eqn. 6.1), where k_R is the rate of ring formation of cyclic monomer and k_P is the rate of

^{73.} Liebnan, J.F.; Greenberg, A. Chem. Rev. 1976, 76, 311.

^{74.} Allinger, N.L.; Tribble, M.T.; Miller, M.A.; Wertz, D.H. J. Am. Chem. Soc. 1971, 93, 1637.

^{75.} Galli, C.; Mandolini, L. Eur. J. Org. Chem. 2000, 3117.

^{76.} Ziegler, K. in *Methoden der Organischen Chemie (Houben-Weyl), Vol 4/2*, Müller, E. (Ed), Georg Thieme Verlag, Stuttgart, **1955**.

^{77. (}a) Hunsdiecker, H.; Erlbach, H. Chem. Ber. 1947, 80, 129; (b) Stoll, M. Helv. Chim. Acta 1947, 30, 1393.

^{78.} Illuminati, G.; Mandolini, L.; Masci, B. J. Am. Chem. Soc. 1977, 99, 6308.

^{79.} Galli, C.; Mandolini, L. Gazz. Chim. Ital. 1975, 105, 367.

formation of cyclic dimer. If the initial concentration is less than unity ($\alpha < 1$), the yield is not less than 55%. For medium rings, $k_{\rm R}/k_{\rm P}$ should be < 0.1 M.⁸⁰

$$\frac{C_{\alpha}}{M_{o}} = \frac{1}{2\alpha} \ln (1 + 2\alpha) \text{ where } \alpha = \frac{M_{o}}{k_{R}/k_{P}} \qquad 6.1$$

and $k_{\rm R}$ and $k_{\rm P}$ are defined by:

monomer
$$\xrightarrow{k_{\rm R}}$$
 monomeric complex 2 monomer $\xrightarrow{k_{\rm P}}$ dimer

Similarly, the parameter η_c/η_m (the yield of cyclic substance obtained by high dilution conditions, Eqn. 6.2) can be used, where η_m is the total number moles of bifunctional substrate, η_c is the number of moles of monomeric ring product produced, and v_f is the constant feed rate in that is measured in mol L⁻¹ sec^{-1.79} The dimensionless parameter β is a measure of the feed rate, and the relative formation of cyclic monomer is a function of the feed rate.⁷⁹

$$\frac{\eta_{\rm c}}{\eta_{\rm m}} = \frac{2}{1 + R(1 + 9n_{\rm f}k_p/k_R 2)} = \frac{2}{1 + R(1 + 8\beta)}$$
 6.2

The dependence on ring size for lactone formation is illustrated by Figure 6.3a (the reactivity for lactone formation), Figure 6.3b (the ΔH^{\ddagger} profile for lactone formation) and Figure 6.3c (the ΔS^{\ddagger} profile for lactone formation).⁶⁹ The quantity $\Delta H^{\ddagger}_{intra} - \Delta H^{\ddagger}_{inter}$ is a useful measure of the strain energies involved in ring formation of lactones. As the chain length increases, ΔH^{\ddagger} decreases.⁸¹ For very large rings (C₁₈-C₂₃), $\Delta H^{\ddagger}_{intra} \approx \Delta H^{\ddagger}_{inter}$ and the intramolecular reaction is nearly strain free. In the C₃-C₁₆ region, ring formation is strain dependent with ΔH^{\ddagger} maximal at C₃ and C₈ (\approx 8 kcal/mol⁻¹ mol⁻¹; 33.5 kJ mol⁻¹). For C₃-C₈, the cis conformation predominates due to the increased strain inherent to a trans conformation.



Figure 6.3. For lactone formation: (a) Reactivity profile, (b) ΔH^{\ddagger} profile, and (c) ΔS^{\ddagger} profile. [Reprinted with permission from Illuminati, G.; Mandolini, L. *Accts. Chem. Res.*, **1981**, 14, 95. Copyright © 1981 American Chemical Society.]

^{80.} Illuminati, G.; Mandolini, L.; Masci, B. J. Am. Chem. Soc. 1974, 96, 1422.

^{81.} Mandolini, L. J. Am. Chem. Soc. 1978, 100, 550.

As shown in Figure 6.3(c), ΔS^{\ddagger} does not show a regular pattern, but more favorable for large rings because of a "looseness in the ring due to low frequency out of plane bending motions".^{69,82} The variation in ΔS^{\ddagger} indicates the importance of individual ring features, with maxima occurring at ring sizes of C₈, C₁₂, and C₁₆. For ring sizes of C₃-C₆, the ΔS^{\ddagger} values are relatively insensitive to ring size. Solvation around the reactive end plays a major role in C₃ and C₄ rings, but for C₅ rings and larger, such solvation is less important.

MOLECULAR MODELING: Lactone Hydrolysis

In aqueous solution, cyclic lactones are in equilibrium with open chain hydroxycarboxylic acids. Equilibrium favors the five-member ring γ -butyrolactone over 4-hydroxybutanoic acid, but favors 10-hydroxydecanoic acid over the nine-member ring nonalactone.



Obtain structures and energies for both lactone and open chain hydroxycarboxylic acid forms of both compounds as well as for the corresponding tetrahedral intermediates (six calculations in total). For each calculation following the first, *click* on > tab at the top of the screen and select **Continue**. This will give you a fresh builder palette and keep this text on screen. Calculate the energy of loss of hydroxide from the five-member ring intermediate *relative* to that for the tenmember ring intermediate (hydroxide will cancel). Which reaction is favored? Calculate the energy of protonation of the five-member ring intermediate *relative* to that for the tenmember ring intermediate (proton will cancel). Which reaction is favored? Are your results consistent with what is observed? Elaborate.

6.6.B.ii. Synthetic Approaches to Macrocyclic Lactones.⁸³ There are many examples of biologically important, naturally occurring lactones. High dilution techniques can be used, as mentioned above. In the final step of a synthesis of amphidinolide P, Trost and co-workers simply heated a dilute solution of **206** in hexane to give an 84% yield of amphidinolide P (**207**).⁸⁴ In this reaction, the eight-membered ring lactone was opened to give a seco-acid, which closed to the macrocyclic lactone, and the hydroxyl group remaining from the eight-membered ring lactone attacked the ketone moiety to generate the hemi-ketal unit in **207**.

^{82.} O'Neal, H.E.; Benson, S.W. J. Chem. Eng. Data 1970, 15, 266.

For a review of macrolactonization in the total synthesis of natural products, See (a) Parenty, A.; Moreau, X.; Campagne, J.-M. *Chem. Rev.* 2006, 106, 911. Also see (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 402-403. For a review of syntheses of medium-sized ring lactones, see Shiina, I. *Chem. Rev.* 2007, 107, 239.

^{84.} Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. J. Am. Chem. Soc. 2005, 127, 17921.



A variety of cyclization techniques have been developed, but all are based on the idea that the carbonyl end of a ω -substituted acid is activated to facilitate attack by or at the other functionalized end. In one example, trifluoroacetic anhydride reacted with **208** to form mixed anhydride **209**, which activated the carbonyl to attack by the hydroxyl moiety and gave **210** in 31% yield, in the Taub et al. synthesis of zearalenone.⁸⁵ Cyclization has also been observed using a mixture of trifluoroacetic acid and trifluoroacetic anhydride.⁸⁶ The use of 2-methyl-6-nitrobenzoic anhydride and dimethylaminopyridine with powdered molecular sieves, the so-called **Shiina macrolactonization**, has also been reported.^{85cd}



Another macrocyclization technique has been developed based on formation of a mixed anhydride. In the **Yamaguchi protocol**⁸⁷ a seco acid is treated with 2,4,6-trichlorobenzoyl chloride, and the resulting mixed anhydride is heated with DMAP (4-*N*,*N*-dimethylamino-pyridine) in toluene. In the Ghosh and Gong synthesis of amphidinolide W, for example, seco-acid **211** was converted to lactone **212** in 50% yield using the Yamaguchi protocol.⁸⁸ The methyl group epimerized and a 1:1 mixture of epimers was isolated in this instance. A variation of this procedure prepares the mixed anhydride by reaction of the seco-acid with Boc anhydride (see Chap. 7, Sec. 7.3.C.iii.), followed by heating with DMAP in toluene.⁸⁹

- 88. Ghosh, A. K.; Gong, G. J. Org. Chem. 2006, 71, 1085.
- 89. Nagarajan, M.; Kumar, V.S.; Rao, B.V. Tetrahedron 1999, 55, 12349.

 ⁽a) Taub, D.; Girotra, N.N.; Hoffsommer, R.D.; Kuo, C.H.; Slates, H.L.; Weber, S.; Wendler, N.L. *Tetrahedron 1968*, *24*, 2443; (b) *Idem J. Chem. Soc. Chem. Commun. 1967*, 225; (c) Shiina, I.; Kubota, M.; Oshiumi, H.; Hashizume, M. J. Org. Chem. *2004*, *69*, 1822. (d) Wu, Y.; Yang, Y.-Q. *J. Org. Chem. 2006*, *71*, 4296. For an example taken from a synthesis of lejimalide B, see Schweitzer, D.; Kane, J.J.; Strand, D.; McHenry, P.; Tenniswood, M.; Helquist, P. Org. Lett. *2007*, *9*, 4619.

^{86.} Baker, P.M.; Bycroft, B.W.; Roberts, J.C. J. Chem. Soc. C, 1967, 1913.

 ⁽a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. Bull. Chem. Soc. Jpn., 1979, 52, 1989; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 710-711.



Mercuric trifluoroacetate [Hg(OCOCF₃)₂] is an effective reagent for the cyclization of hydroxy thio-esters.⁹⁰ Masamune et al. used this cyclization procedure for the conversion of **213** to **215** (in 90% yield) in a synthesis of zearalenone dimethyl ether.⁹¹ Masamune developed this procedure (the **Masamune protocol**) to complete the total synthesis of methymycin, where one step involved treatment of a thioester with mercuric salts.^{92,91} Mercury(II) has an affinity for bivalent sulfur and it binds the thioester unit as well as the terminal hydroxyl group, as in **214**. This coordination brings the reactive termini in **216** [HO and S(R)C=O] into close proximity, and the hydroxyl oxygen can attack the carbonyl carbon of the thioester to give cyclized product, lactone **213**. Thioester **213** was formed from the corresponding phosphonate ester of the acid. A carboxylic acid is first converted to the phosphonate ester, represented by generic structure **216**. Subsequent reaction of **216** with the thallium salt of 2-methyl-2-propanethiol [TISC(Me)₃] gave **217**. This generic example shows a mild and general procedure for the preparation of thioesters, and was used to prepare **213**.



Diethyl azodicarboxylate (EtO₂C–N=N–CO₂Et, DEAD) is a key reagent in the Mitsunobu

^{90.} Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. J. Am. Chem. Soc. 1975, 97, 3513.

^{91.} Masamune, S.; Kamata, S.; Schilling, W. J. Am. Chem. Soc. 1975, 97, 3515.

^{92.} Masamune, S.; Kim, C.U.; Wilson, K.E.; Spessard, G.O.; Georghiou, P.E.; Bates, G.S. J. Am. Chem. Soc. 1975, 97, 3512.

reaction (sec. 2.6.A.ii) and has also been used for macrolactonization.⁹³ A synthetic example is the reaction of **218** with DEAD, and PPh₃, which gave a 73% yield of **219** in Steglich and coworker's synthesis of ornatipolide.⁹⁴ A variety of specialized reagents have



been developed for macrolactonization reactions. Several of these reagents are effective for the cyclization of ω -hydroxy acids, as shown in Table 6.1. For comparison, results for cyclization with DEAD and **222** are included, for conversion of a hydroxy acid to lactone **204**. The **Corey-Nicolaou reagent**⁹⁵ (2,2'-dipyridyl disulfide, **220**) and the **Mukaiyama reagent**⁹⁶ (2-chloro-1-methyl-pyridinium iodide, **221**) are two of the more important. A number of related reagents have been developed, including imidazole disulfide **222** [2,2'-dithio-(4-*tert*-butyl-1-isopropylimidazole)]⁹⁷ and imidazole **223** [*N*-(trimethylsilyl)imidazole].⁹⁸ As seen in Table 6.1, diolide (**224**) can be formed by reaction of an initial intermolecular coupling product, the ω -substituted carboxylate [X-(CH₂)_n-CO₂-(CH₂)_nCO₂⁻]. The nucleophilic oxygen anion of the carboxylate group displaces the X leaving group in a macrolactonization process to give the diolide (see **224**). Diolides are commonly observed during the formation of medium size lactones where transannular interactions lead to poor yields. Cyclization to form a 10-membered lactone is difficult, for example, and under high dilution conditions the formation of the 20-membered diolide is usually favored. Indeed, diolides are common contaminants in reactions that form 6- to 11-membered ring lactones.



^{93.} Kurihara, T.; Nakajima, Y.; Mitsunobu, O. Tetrahedron Lett. 1976, 2455.

^{94.} Ingerl, A.; Justus, K.; Hellwig, V.; Steglich, W. Tetrahedron 2007, 63, 6548.

^{95. (}a) Corey, E.J.; Nicolaou, K.C. J. Am. Chem. Soc. 1974, 96, 5614. The actual cyclization has been called the Corey-Nicolaou macrocyclization, (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 184-185.

^{96.} Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. For a synthetic example taken from a synthesis of the sorangiolides, see Das, S.; Abraham, S.; Sinha, .C. *Org. Lett.* **2007**, *9*, 2273.

^{97.} Corey, E.J.; Brunelle, D.J. Tetrahedron Lett. 1976, 3409.

^{98.} Bates, G.S.; Diakur, J.; Masamune, S. Tetrahedron Lett. 1976, 4423.

$(CH_2)_n \longrightarrow (CH_2)_n $										
n	Reagent	<u>% 204</u>	<u>% 234</u>	<u>n</u>	Reagent	<u>% 204</u>	<u>% 234</u>			
5	220	71	7	11	220	66	7			
	221	89	0		221	69	14			
	DEAD	40	53		222	87				
6	221	0	93		DEAD	60	17			
7	220	8	41	12	220	68	6			
	221	13	34	13	222	90				
	DEAD	0	20	14	220	80	5			
10	220	47	30		221	84	3			
	221	61	24	15	222	96				

 Table 6.1.
 Macrolactonization of ω-Hydroxy Acids

The Corey-Nicolaou procedure reacted **220** with a seco acid to form a thioester (**225**), which is in equilibrium with the protonated form. Hydrogen bonding leads to a template effect (see **226**), that allows nucleophilic acyl attack by the hydroxy group to give **227**. Displacement of thiopyridone (**228**) gives the lactone (**204**). A synthetic example that used **220** converted **229** to **230**, in 62% yield, in Kang and co-worker's synthesis of (+)-pamamycin-607.⁹⁹ The addition of cupric bromide in a second step facilitated the macrocyclization.¹⁰⁰



Another useful reagent is 1,1'-carbonyldiimidazole (232). Hydroxyacid 231 was converted to 233 (40% yield) in White and co-worker's model studies for a synthesis of erythromycin

^{99.} Kang, S.H.; Jeong, J.W.; Hwang, Y.S.; Lee, S.B. Angew. Chem. Int. Ed., 2002, 41, 1392. 100. Kim, S.; Lee, J.I. J. Org. Chem. 1984, 49, 1712.

B.¹⁰¹ This reagent promotes formation of an initial imidazolium intermediate to activate the carbonyl to attack. White also cyclized **231** by treatment with tosyl chloride and triethylamine under dilute conditions (0.01-0.02 M), and obtained a 52% yield of **233**.¹⁰¹



Dibutyltin oxide (*n*-Bu₂SnO) was reported to be a tin-template driven extrusion lactonization reagent.^{102a,b} This reagent effects cyclization in refluxing mesitylene with an ω -hydroxy acid, giving 22-63% of the corresponding 13-17 membered ring lactone (0% for n = 7, 63% for n = 14 and 60% for n = 15). The reaction works via formation of **234**, where the tin reagent complexes the carbonyl unit and the hydroxyl group (as in **235**).



Thermally induced loss of water is accompanied by extrusion of n-Bu₂SnO to give the lactone, **236**. The reaction requires stoichiometric amounts of dibutyltin oxide to ensure reasonable reaction times. The reagent does not induce racemization at the stereogenic center bearing the hydroxyl group, so it is amenable to asymmetric macrolactonization. Cyclization of **237** to **238**, for example, proceeded in 44% yield and was used in Hanessian and co-workers synthesis of ricinelaidic lactone.¹⁰²



^{101.} White, J.D.; Lodwig, S.N.; Trammell, G.L.; Fleming, M.P. Tetrahedron Lett. 1974, 3263.

^{102. (}a) Steliou, K.; Szczygielska-Nowosielska, A.; Favre, A.; Poupart, M.A.; Hanessian, S. J. Am. Chem. Soc. 1980, 102, 7578; (b) Steliou, K.; Poupart, M.A. Ibid. 1983, 105, 7130; (c) Shanzer, A.; Mayer-Shochet, N.; Frolow, F.; Rabinovich, D. J. Org. Chem. 1981, 46, 4662; (d) Shanzer, A.; Libman, J.; Gottlieb, H.E. Ibid. 1983, 48, 4612.

Trost and co-workers reported another macrolactonization method. Reaction of ω -hydroxy acid **239** with ethoxyethyne and the ruthenium catalyst shown was followed by treatment with camphorsulfonic acid in dilute solution to give a 69% yield of **240**.¹⁰³ This two-stage macrolactonization protocol is effective for generating 14-membered rings and larger, and does not involve treatment with base.



It is useful to note that the yield of macrocyclic product usually depends upon the method used. Clearly, there are several reagents that one can use for this reaction, and the choice is dictated by the ease of reaction and the yield. This is illustrated in a synthesis of (–)-spinosyn A, reported by Frank and Roush.¹⁰⁴ Cyclization of seco-acid **241** with the Mukaiyama reagent (**221**) or under Yamaguchi conditions gave relatively poor yields of macrocycle **242**. Mitsunobu conditions gave better results, using either diethyl azodicarboxylate or diisopropyl azodicarboxylate. Significant amounts of hydrazide were formed using the standard Mitsunobu conditions.¹⁰⁴ The use of DIAD (diisopropylazodicarboxylate) for suppression of this side-product had been reported in the literature,¹⁰⁵ but the yield of **242** was diminished. The use of yet another coupling reagent PyBOP (benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate)¹⁰⁶ gave the best results, although the related PyBrOP¹⁰⁷ gave significantly poorer results.



^{103.} Trost, B.M.; Chisholm, J.D. Org. Lett. 2002, 4, 3743.

^{104.} Frank, S.A.; Roush, W.R. J. Org. Chem. 2002, 67, 4316.

^{105.} Evans, D.A.; Ratz, A.M.; Huff, B.E.; Sheppard, G.S. J. Am. Chem. Soc. 1995, 117, 3448.

^{106.} Coste, J.; Frérot, E.; Jouin, P.; Castro, B. Tetrahedron Lett. 1991, 32, 1967.

^{107.} Frérot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P. Tetrahedron 1991, 47, 259.

6.7. CONCLUSION

The intent of this chapter was to tie together many of the principles introduced in earlier chapters. In addition, many of the principles used in the important chapters dealing with making carboncarbon bonds have been discussed. If there is a theme to this chapter, it is that organic chemists can exercise a significant amount of control over synthetic reactions by understanding the mechanism of the trans-formations and the various interactions of heteroatoms and reagents. A thorough understanding of the conformational aspects of reactivity is essential. With knowledge of these principles, a useful plan can be assembled for the synthesis of even complex molecules. Without this understanding, syntheses beyond a few simple steps will be difficult.

One last piece of information is required for synthesis in order to manipulate functional groups. In those cases where a heteroatom functional group interferes with a transformation and cannot be removed, modified, or inserted earlier or later in a synthesis, methods are available to temporarily block it. This method is termed protection and the moiety used to block the reactive fragment is called a protecting group, which will be the focus of Chapter 7.

HOMEWORK

1. In each of the following, give the major product and classify each reaction according to Baldwin's rules:



2. Explain why the following sequence results in inversion of configuration of the hydroxyl group:



3. Explain this transformation by giving the three intermediate products.



For related reactions see (a) Fieser, L.F.; Fieser, M. *Advanced Organic Chemistry*, Reinhold, New York, **1961**, pp 897-898; (b) *Technol. Repts. Osaka Univ.*, **1958**, *8*, 455 [*Chem. Abstr.*, **1959**, 53: 18920i].

4. Draw the major product of this reaction and predict the correct stereochemistry. Briefly explain your answer.

5. Explain why these two saponification reactions lead to different products (ring closed vs. ring opened).



6. Suggest a reason why the carboethoxy group epimerizes upon treatment with potassium carbonate. Why is the second step required?



7. Offer a mechanistic rationale for the following conversion that explains the stereoselectivity of the reaction.



8. Show the structure of both A and B. Each of these reactions has a name associated with it. Give the name of each reaction and look up one recent review of each.



9. Predict the major product of this reaction. Explain your answer in the context of other possible products.



- 10. Inspection of Table 6.1 suggests that the Mukaiyama reagent gives better yields of lactone with simple ω -hydroxy acids than the Corey-Nicolaou reagent. Offer an explanation that accounts for this observation.
- 11. Give the major product of the following reactions:


12. In each case provide a suitable synthesis. Show all intermediate products and all reagents.



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Protecting Groups

7.1. INTRODUCTION

chapter

Many problems arise during a synthesis. Some synthetic targets contain more than one functional group, and if they interact with each other or if one group reacts with a reagent competitively with another group, the synthesis can be in serious trouble. The presence of a ketone and an aldehyde in the same molecule at the same time is an obvious point of concern, since they react similarly with nucleophilic species such as a Grignard reagent. Aldehydes are generally more reactive, but the difference in rate may be insufficient to make the reaction chemoselective. The presence of an alcohol and an amine in the same molecule at the same time will also cause problems since reactions with acids, bases, and nucleophiles are possible for both functional groups. One practical solution to such problems is to temporarily block a reactive position by transforming it into a new functional group that will not interfere with the desired transformation. That blocking group is called a **protecting group**. Incorporating a protecting group into a synthesis requires at least two chemical reactions, however. The first reaction transforms the interfering functional group into a different one that will not compete with the desired reaction, and is termed **protection**. The second chemical step transforms the protecting group back into the original group at a later stage of the synthesis. This latter process is termed deprotection.

Is the use of a protecting group a desirable feature that should always be incorporated into a synthesis? *No*, it should always be avoided if possible. In many cases, however, it *cannot* be avoided and a discussion of where to anticipate the use of a protecting group in a synthesis is necessary.¹ As mentioned above, the process of protection-deprotection adds two steps to a synthesis. If there are four interfering functional groups and each requires protection, as many as eight steps may be added. Planning the order for insertion of a given functional group can usually minimize the use of protecting groups, but not always. If an aldehyde group can be inserted into a molecule after a ketone-Grignard reaction has been done, for example, there is no need to protect the aldehyde and two synthetic steps are saved. When a protection step is necessary, the first question is what transformation can block the reactivity of a given group but provide a chemical pathway back to the original group in high yield. The protecting group

^{1.} For protecting group strategies in organic synthesis see Schelhaas, M.; Waldmann, H. Angew. Chem. Int. Ed. 1996, 35, 2056.

must be relatively inert and ideally react with a specific reagent to unmask it (i.e., regenerate the original group).

The most important functional groups that cause reactivity problems are alcohols, ketones and aldehydes, and amines. Carboxylic acids contain the COOH group, which can also cause problems, and this is often blocked as an ester. For alcohol groups, the acidic hydrogen of the O-H causes problems, and a protecting group must remove that hydrogen. The acidic hydrogen can be temporarily removed by conversion of the alcohol to an ether, an acetal or an ester. Ketones and aldehydes undergo nucleophilic acyl addition, and the carbonyl moiety is usually protected by conversion to an acetal or a ketal, a thioacetal or a thioketal, or a hydrazone derivative. The interfering part of an amine is the basic, lone pair of electrons. These electrons can be tied up by conversion to a quaternary ammonium salt, but such salts are not always easy to use in synthetic sequences. The lone pair is not actually removed, but electronically delocalized by conversion to an amide or a sulfonamide. In some reactions, the N-H group is acidic, and a protecting group must block the acidic hydrogen.

If a protecting group is to be used, methods must be known to protect the functional group in high yield, and the deprotection must be done with some selectivity, also in high yield. The excellent monographs by Wuts and Greene describe protection for these functional groups as well as many others in great detail.² Other books that focus on the nature and use of protecting groups in organic chemistry are also available.³ The series *Compendium of Organic Synthetic Methods*⁴ also provides some examples of recently used protecting groups, and there are reviews,⁵ including the use of protecting groups in combinatorial synthesis (see sec. 10.12).⁶

Two essential questions remain. When does one use a protecting group and how is that group

 ⁽a) Greene, T.W. Protective Groups in Organic Synthesis Wiley, New York, 1980; (b) Wuts, P.G.M.; Greene, T.W. Protective Groups in Organic Synthesis 2nd ed., Wiley, New York, 1991; (c) Wuts, P.G.M.; Greene, T.W. Protective Groups in Organic Synthesis 3rd ed., Wiley, New York, 1999; (d) Wuts, P.G.M.; Greene, T.W. Protective Groups in Organic Synthesis 4th ed., Wiley, New Jersey, 2006.

 ⁽a) Kocienski, P.J. Protecting Groups, 3rd ed., Georg Thieme Verlag; 2005; (b) Curti, L.; Czsko, B. Strategic Applications of Named reactions in Organic Synthesis, Academic Press, 2005; (c) Li, J.J. Name Reactions: A Collection of Detailed Reaction Mechanisms, 2nd ed., Springer, 2003; (d) Robertson, J. Protecting Group Chemistry, Oxford University Press, 2000; (e) Hanson, J.R. Protecting Groups in Organic Synthesis, Blackwell Pub., 1999.

Smith, M.B. Compendium of Organic Synthetic Methods, Vol. 11, Wiley, New York, 2003; Vol. 10, 2002; Vol. 9, 2000; Vol. 8, 1995; Vol. 7, 1992; Vol. 6, 1988. Also see Volumes 1-5 of this series, initiated by Harrison, I. and Harrison, S (Wiley).

 ⁽a) Jarowicki, K.; Kocienski, P. J. Chem. Soc. Perkin Trans. 1 1999, 1589; (b) Jarowicki, K.; Kocienski, P. J. Chem. Soc. Perkin Trans. 1 2000, 2495; (c) Sartori, G.; Ballini, R.; Bigi, F.; Bosica, G.; Maggi, R.; Righi, P. Chem. Rev. 2004, 104, 199.

 ⁽a) Singh, A.K.; Weaver, R.E.; Powers, G.L.; Rosso, V.W.; Wei, C.; Lust, D.A.; Kotnis, A.S.; Comezoglu, F.T.; Liu, M.; Bembenek, K.S.; Phan, B.D.; Vanyo, D.J.; Davies, M.L.; Mathew, R.; Palaniswamy, V.A.; Li, W.-S.; Gadamsetti, K.; Spagnuolo, C.J.; Winter, W.J. Org. Process Res. Dev. 2003, 7, 25; (b) Orain, D.; Ellard, J.; Bradley, M. J. Comb. Chem. 2002, 4, 1.

chosen? When to use a protecting group is not an easy question to answer. Wuts and Greene' books are an excellent source for choosing a protecting group, and they provide many examples. Section 7.2 will outline problems where the best solution was to use a protecting group, and Section 7.3 will give a brief review of common protecting groups. It is important to note that there are other uses for the groups labeled here as protecting groups. Such groups can be used to provide directing effects, influence solubility and other physical properties, make it easier to isolate certain products, and they can increase the crystallinity of a compound. In addition, protected functional groups are common in the pharmaceutical industry as prodrugs. They are useful for solid-phase attachment of functional groups (see sec. 10.12), and for tagging molecules (fluorescence tagging for example). Some of these uses will be touched upon in later chapters, but this chapter will focus on classical uses for protecting groups.

7.2. WHEN ARE PROTECTING GROUPS NEEDED?

There is no convenient set of rules that outline when to use protecting groups. Each synthesis is different, and the requirements vary with the reaction sequence and functional groups that are present. In this section, a series of common synthetic problems will be presented where protection-deprotection was a viable solution.

The place to begin this discussion is with a synthesis. An analysis of diol **1** shows that there are several possible disconnections, but we will focus on the CHOH-hexyl bond. Disconnection of the indicated bond leads to disconnect products **2** and **3**. Using the concept of synthetic equivalents introduced in chapter 1, the disconnect products are converted to hexylmagnesium halide (**4**, sec. 8.4.C), and a β -hydroxyaldehyde (**5**). If this synthetic route is chosen, protecting groups are necessary.

$$\stackrel{n-C_{6}H_{13}}{\overset{\flat}{\underset{OH}{\longrightarrow}}} \stackrel{OH}{\underset{I}{\longrightarrow}} \stackrel{OH}{\underset{OH}{\longrightarrow}} \stackrel{a}{\underset{OH}{\longrightarrow}} \stackrel{OH}{\underset{3}{\longrightarrow}} \stackrel{a}{\underset{OH}{\longrightarrow}} \stackrel{OH}{\underset{3}{\longrightarrow}} \stackrel{a}{\underset{OH}{\longrightarrow}} \stackrel{OH}{\underset{3}{\longrightarrow}} \stackrel{a}{\underset{OH}{\longrightarrow}} \stackrel{OH}{\underset{OH}{\longrightarrow}} \stackrel{A}{\underset{OH}{\longrightarrow}} \stackrel{A}{\underset{OH}{\longrightarrow}} \stackrel{OH}{\underset{OH}{\longrightarrow}} \stackrel{A}{\underset{OH}{\longrightarrow}} \stackrel{A}{\underset{OH}{\longrightarrow} \stackrel{A}{\underset{OH}{\longrightarrow}} \stackrel{A}{\underset{OH}{\longrightarrow}} \stackrel{A}{\underset{OH}{\longrightarrow} \stackrel{A}{\underset{OH}{\longrightarrow}} \stackrel{A}{\underset{OH}{\longrightarrow} \stackrel{A}{\underset{OH}{\longrightarrow}} \stackrel{A}{\underset{OH}{\longrightarrow}} \stackrel{A}{\underset{OH}{\longrightarrow} \stackrel{A}{\underset{OH}{\longrightarrow}} \stackrel{A}$$

Why is it necessary to use a protecting group? Grignard reagent **4** is a base as well as a nucleophile, and attempts to react it with **5** may cause problems because the acidic proton of the hydroxyl group reacts faster than the Grignard reagent adds to the carbonyl. The alkoxide formed by reaction of the OH can react with a second equivalent of Grignard reagent, of course, but there are problems of solubility because the alkoxide is rather polar. In general, it is probably easier to block the OH to prevent the deprotonation. The O-H unit of **5** must be replaced with a functional group that can tolerate the Grignard reaction, but that group must undergo a chemical reaction to convert it back to a hydroxyl. If the hydroxyl group is converted to an ether, as in **6**, the key Grignard reaction can proceed to give **7**. In a subsequent step, the R group can be removed to regenerate the hydroxyl moiety in **1**. In this case, the hydroxyl group was protected, allowing the desired reaction to proceed.

$$H \underbrace{\bigcirc}_{O} \underbrace{\frac{1.n - C_6 H_{13} - MgX}{2. H_3 O^+}}_{\mathbf{6}} \underbrace{n - C_6 H_{13}}_{\mathbf{7} OH} \underbrace{\stackrel{OR}{}_{\text{Lewis acid}}}_{\mathbf{7} OH} \underbrace{\stackrel{OH}{}_{\mathbf{1} OH}}_{\mathbf{1} OH}$$

Kitching and co-worker's synthesis of a gland secretion of fruit flies provides a synthetic solution for the preparation of **1**, in which 1,3-propanediol was converted to the tetrahydropyranyl (THP) derivative **8** by reaction with dihydropyran.⁷ The identical nature of the two hydroxyls made protection of one very easy, by simply controlling the stoichiometry of the reagent. Oxidation of the unprotected alcohol gave aldehyde **9**, and subsequent addition of hexylmagnesium bromide gave **10**. Deprotection with acidic methanol gave the product, 1,3-nonanediol (**1**). This particular sequence was used to prepare an authentic sample of a synthetic intermediate for purposes of comparison, and no yields were reported. When a disubstituted molecule is symmetrically functionalized (as with 1,3-propanediol), the two groups are chemically equivalent and protection of one of them is rather easy. The reagents used in the remainder of the synthesis will determine the choice of protecting group.

In many syntheses, protection must be used or the sequence will not work, but what are the consequences of using protecting groups in synthesis? One price to be paid is at least two synthetic steps (insertion and removal of the protecting group) that must be added to the sequence, and the overall yield of the synthesis will suffer accordingly. The ability to generate a target directly must be compared to the loss of material that accompanies the use of protecting groups, and each route evaluated in the context of the specific synthesis. Usually, protecting groups are used because there is no direct way to solve the problem without them.

In complex synthetic targets, it is common for two or more identical functional groups to be present. It maybe difficult to incorporate all of those groups simultaneously, and there is a chance that once two groups are incorporated, one will interfere with reactions aimed at another. A synthesis of sigialomycin D by Danishefsky and Geng provides an example where several alcohol moieties are incorporated in a molecule.⁸ A description of the specific protecting groups presented in this example will be presented later in this chapter, but an analysis of the strategy will illustrate how their use led to the desired target. The synthesis begins with D-2-deoxyribose **11**. Protection of the diol unit allowed ring-opening to a hydroxy-aldehyde, protection of the primary alcohol as the pivaloyl ester, Wittig reaction to extend the carbon chain and hydroboration gave alcohol **12**. Protection of the diol unit in **11** was essential,

^{7.} Kitching, W.; Lewis, J.A.; Perkins, M.V.; Drew, R.; Moore, C.J.; Schuring, V. König, W.A.; Francke, W. J. Org. Chem. 1989, 54, 3893.

^{8.} Geng, X.; Dainishefsky, S.J. Org. Lett. 2004, 6, 413.

because 12 contains four OH units and three are protected so that only one will participate in the next sequence. A series of five reactions converted 12 to 13, and the OH unit was protected as a silyl ether, allowing selective deprotection of the pivaloyl ester to give 14. In three steps, 14 was converted to alkyne-ester 14. Again, careful choice of protecting groups and the order in which groups are incorporated allowed first one side of the molecule to be elaborated, and then the other. Ester 15 was converted to lactone 16 in three steps, and another three steps were required to incorporate the aromatic ring system (see 17) that contained two protected phenolic units. The choice of the silyl ether protecting group allowed that alcohol to be unmasked in 17, and Martin's sulfurane conditions⁹ converted the benzylic alcohol in 17 to the C=C unit in 18. Finally, acid hydrolysis converted the dioxolane group in 18 to the diol, a structural component of sigialomycin D (19). This sequence illustrates that a sugar derivative can be manipulated in such a way that two of the hydroxyl groups are carried throughout the synthesis, in protected form, to the final product 19. Other alcohol units are incorporated and used along the way, and each is protected with a group that allows that OH group to be deprotected and used a the proper



^{9.} Martin, J.C.; Arhart, R.J. J. Am. Chem. Soc. 1971, 93, 4327.

time. Despite the need for protection and deprotection, this sequence allowed Danishefsky to incorporate specific functional groups in a controlled manner and in the desired sequence, one of the positive aspects of using protecting groups.

If protecting groups must be used in a synthesis, the goal is to be efficient and keep the number of steps to a minimum. It is often necessary to protect a group, deprotect it, and then later protect it a second time. If these steps could somehow be combined, it could save on the total number of steps in the synthesis and make the overall process more efficient. An example that illustrates this type of efficiency is the conversion of **20** to **23** in Silverstein's synthesis of α -cubebane.¹⁰ In this case, the starting material is **20**, which contains two primary hydroxyl groups that are first protected as a ketal in **21**. This choice allows manipulation of **21** to give **22** where a third hydroxyl group has been incorporated. The next step in the sequence required manipulation of the –CH₂OH unit that is adjacent to the methyl group. Rather than deprotect **22** and then re-protect the resulting triol, **22** was treated with acid and that induced deprotection of the seven-membered ring ketal and formation of the more stable five-membered ring ketal moiety in **23**. Understanding the stability of the two ketals allowed Silverstein and co-workers to maximize the utility of the protecting group, and minimize the number of steps in the synthesis.



There are occasions when it is impossible to avoid placing two like functional groups in a molecule, yet one of them is to be selectively transformed and the other must be protected. The groups can be incorporated at different times in the synthesis. The conversion of **11** to **19** illustrated this concept. Alternatively, *if* one functional group reacts at a different rate in the protecting group reaction selectivity may be achieved. Amino alcohol **24** is a molecule that contains two functional groups that can interfere with each other, and it was necessary to incorporate both at the same time (from an amino acid precursor) in Andersen and Globe's synthesis of kessanol.¹¹ The functional groups are different, an amino group and a hydroxyl group and protection of either the OH or the NH₂ selectively requires chemical differentiation. The hydroxyl group was to be converted to aldehyde **26**. Apart from the fact that OH and NH₂ could compete for a protecting group reagent, the amine unit would interfere with later stages of the planned synthesis. The goal was to protect the amine, allowing manipulation of the alcohol. When **24** was treated with acetic anhydride, both the amine and the alcohol

^{10.} Pearce, G.T.; Gore, W.E.; Silverstein, R.M.; Peacock, J.W.; Cuthbert, R.A.; Lanier, G.N.; Simeone, J.B. J. Chem. Ecol. 1975, 1, 115.

^{11.} Andersen, N.H.; Golec, Jr, F.A. Tetrahedron Lett. 1977, 3783.

formed their respective acetates in **25**. Knowledge that an ester is more easily hydrolyzed than the amide, however, allowed both groups to be protected and the OH unit to be selectively deprotected. Treatment of **25** with aqueous KOH gave the alcohol, which was oxidized to the aldehyde in **26** by **Collins oxidation** (sec. 3.2.B).



A final example illustrates planning a synthesis in such a way that groups that may interfere with each other are protected. The synthesis of **30** from **27**, taken from the Chiang et. al. synthesis of inhibitors of cholesterol biosynthesis,¹² involves conversion of the Me₂C=C group

to an aldehyde that can undergo an olefination reaction. Clearly, the presence of the ketone moiety in **27** would interfere with this sequence. For this reason, a precursor to the aldehyde group in **29** was incorporated early in the sequence, in the form of an alkene because the aldehyde could be unmasked later by oxidative cleavage. Before this step, however, the ketone unit was



protected as the ketal (28) so that ozonolysis of the alkene would give the aldehyde unit in 29. **Horner-Wadsworth-Emmons olefination** (sec. 8.8.A.iii) of this aldehyde gave 30. Knowing that aldehyde and ketone units must be present in the same molecule allowed them to be synthetically incorporated at different times, and in a manner where one would not interfere with the chemistry of the other.

7.3. PROTECTING GROUPS FOR ALCOHOLS, CARBONYLS, AND AMINES

This section will introduce the actual functional group modifications used for protecting groups. The monographs by Wuts and Greene² describe protecting groups for many different functional groups. This section is not exhaustive, but rather representative. Most of the protecting groups used in synthesis involve alcohols, ketones, aldehydes or amines, and only common protecting groups will be examined. The intent is to introduce protecting groups, and to provide a few simple tools that may solve a synthetic problem.

^{12.} Chiang, Y.-C.P.; Yang, S.S.; Heck, J.V.; Chabala, J.C.; Chang, M.N. J. Org. Chem. 1989, 54, 5708.

7.3.A. Protection of Alcohols

Before a protecting group can be developed for a given functional group, the interfering part of that group must be identified. In the case of alcohols, this is almost always the acidic hydrogen of the O–H unit. If an alcohol moiety interferes with a planned reaction, the OH must be converted to O–X (another functional group), but this reaction must proceed in high yield and under mild conditions. The new functional group (now called the **protecting group**) must be impervious to all reagents used in succeeding synthetic steps but must be easily removed in high yield, under conditions that do not disturb other functionality. All of this chemistry must be done within the limitations of reactivity imposed by the given functional group.

Alcohols give two major reactions that largely fit these criteria. Conversion of alcohols to ethers usually proceeds in high yield to give a relatively inert product. Due to this lack of reactivity, the reaction conditions required for cleavage of the ether may be very harsh. Specialized ether protecting groups have therefore been developed that can be removed under mild and selective conditions. Another solution is to convert alcohols to acyclic acetals or ketals. These groups possess much of the inert character of ethers, but are easily converted back to the alcohol. It is also possible to convert alcohols to esters under mild conditions, and hydrolysis easily converts them back to the alcohol. There is a problem if an ester group is used, however, since many reagents react with its acyl carbon. A few examples of ester protecting groups will be discussed, but ethers and acetals constitute the vast majority of alcohol protecting groups.

7.3.A.i. Ether and Acetal Protecting Groups. A simple way to protect the OH of an alcohol is by conversion to its methyl ether (-OMe).¹³ Reaction of an alcohol with a base [often sodium hydride (NaH) in THF or DMF] gives an alkoxide. Subsequent reaction with iodomethane gives the methyl ether via an S_N2 reaction (sec. 2.6.A.i) called the Williamson ether synthesis.¹⁴ Methyl ethers can also be prepared by treatment of an alcohol with trimethyloxonium tetrafluoroborate (Meerwein's reagent),¹⁵ or with dimethyl sulfate (Me₂SO₄),¹⁶ a base and a phase-transfer agent (such as tetrabutylammonium iodide).¹⁷ Methyl ethers are stable to strong bases, nucleophiles, organometallics, ylids, hydrogenation [except for benzylic ethers (see below)], oxidizing agents, and hydride reducing agents. They are stable in the pH range 1 \rightarrow 14. Methyl ethers can be cleaved with concentrated HI, but trimethylsilyl iodide unmasks the alcohol in chloroform at ambient temperatures.¹⁸ Lewis acids such as boron tribromide

^{13.} Reference 2a, pp 14-16, 296-298; Reference 2b, pp 15-17; Reference 2c, pp 23-27; Reference 2d, pp 25-30.

^{14. (}a) Williamson, A.W. J. Chem. Soc. 1851, 4, 229; (b) Dermer, O.C. Chem. Rev. 1934, 14, 409.

^{15. (}a) Meerwein, H.; Hinz, G.; Hofmann, P.; Kroning, E.; Pfeil, E. J. Prakt. Chem. 1937, 147, 257; (b) Earle, M.J.; Fairhurst, R.A.; Giles, R.G.; Heaney, H. Synlett 1991, 728.

^{16. (}a) Merz A. Angew. Chem. Int. Ed. 1973, 12, 846; (b) Reuvers, J.T.A.; de Groot, A. J. Org. Chem. 1986, 51, 4594.

^{17.} Merz, A. Angew. Chem. Int. Ed. 1973, 12, 846.

^{18.} Jung, M.E.; Lyster, M.A. J. Org. Chem. 1977, 42, 3761.

 $(BBr_3)^{19}$ also cleave methyl ethers to alcohols. The use of this group is illustrated in Williams and co-worker's synthesis of paraherquamide A,²⁰ in which vanillin (**31**) was used as a starting material and has the OMe unit present. After six synthetic steps, lactam **32** was treated with boron tribromide to remove the methyl protecting group, giving a 99% yield of **33**.



Another common protecting group is the benzyl ether (–OCH₂Ph, **OBn**),²¹ prepared by reaction of the nucleophilic alkoxide of an alcohol with benzyl bromide or chloride.²² Benzyl ethers are stable to a wide range of reagents including pH 14, carbanions, and organometallics, nucleophiles, hydrides and some oxidizing agents. The two best methods for removing the benzyl group involve cleavage of the O–CH₂Ph bond by hydrogenolysis (secs. 4.8.E, 4.9.D). The most common method is probably catalytic hydrogenation with a palladium catalyst,²³ but hydrogenolysis with sodium or potassium in ammonia (sec. 4.9.D) is also used.²⁴ Wood and co-workers used the *O*-benzyl group in a synthesis of kalihinol C,²⁵ in which the free alcohol in **34** was converted to benzyl ether (**35**) in 93% yield by treatment with sodium hydride (KH) and benzyl bromide. Seven synthetic steps were required to give **36**, which contained the original *O*-benzyl group. Treatment with sodium and ammonia led to deprotection, and formation of **37** in 91% yield.



 ⁽a) Niwa, H.; Hida, T.; Yamada, K. *Tetrahedron Lett.* 1981, 22, 4239; (b) Kuehne, M.E.; Pitner, J.B. J. Org. Chem. 1989, 54, 4553; (c) Grieco, P.A.; Nishizawa, M.; Oguri, T.; Burke, S.D.; Marinovic, N. J. Am. Chem. Soc. 1977, 99, 5773.

20. Williams, R.M.; Cao, J.; Tsujishima, H.; Cox, R.J. J. Am. Chem. Soc. 2003, 125, 12172.

- 22. (a) Dueno, E.E.; Chu, F.; Kim, S.-I.; Jung, K.W. *Tetrahedron Lett.* **1999**, 40, 1843; (b) Iwashige, T.; Saeki, H. *Chem. Pharm. Bull.*, **1967**, 15, 1803.
- 23. (a) Heathcock, C.H.; Ratcliffe, R. J. Am. Chem. Soc. 1971, 93, 1746; (b) Hartung, W.H.; Simonoff, C. Org. React. 1953, 7, 263.
- (a) McClosky, C.M. Adv. Carbohydr. Chem. 1957, 12, 137; (b) Reist, E.J.; Bartuska, V.J.; Goodman, L. J. Org. Chem. 1964, 29, 3725; (c) Schön, I. Chem. Rev. 1984, 84, 287; (d) Zakarian, A.; Batch, A.; Holton, R.A. J. Am. Chem Soc. 2003, 125, 7822.
- 25. White, R.D.; Keaney, G.F.; Slown, C.D.; Wood, J.L. Org. Lett. 2004, 6, 1123.

^{21.} Reference 2a, pp 29-31, 296-298; Reference 2b, pp 47-53; Reference 2c, pp 76-84; Reference 2d, pp 102-106.

Alcohols can be converted to a *tert*-butyl ether²⁶ [O–C(CH₃)₃, **-O-t-Bu**] by reaction of the alcohol with 2-methyl-2-propene (isobutylene) and an acid catalyst (sulfuric acid or BF₃).²⁷ This procedure takes advantage of the facile formation and relative stability of a tertiary cation, which allows subsequent reaction with the alcohol in a S_N1 type reaction (sec. 2.6.B) to give the ether. A limitation on this reaction is that other functionality in the molecule must be compatible with acidic conditions. As a protecting group, *tert*-butyl is stable to pH 1 \rightarrow 14, as well as to nucleophiles, organometallics, hydrides, catalytic hydrogenation, oxidations and dissolving metal reductions. The group can be removed with strong aqueous acid (< pH 1), as well as with Lewis acids. Two common methods for removal of the *tert*-butyl group are treatment with anhydrous trifluoroacetic acid (CF₃COOH, TFA)^{27a} or with trimethylsilyl iodide.¹⁸

Commonly, incorporation or removal of methyl, benzyl, *tert*-butyl and other simple ether protecting groups is incompatible with the presence of sensitive functional groups elsewhere in the molecule. In the case of alcohols, a molecule may contain several hydroxyl moieties that require protection and subsequent deprotection in a specific order. Several ether-like protecting groups have been developed that show greater selectivity in reactions with acids or Lewis acids, allowing more latitude in the choice of a method to remove them. Wuts and Greene classified these alternatives as substituted methyl ethers, but their RO–CHR¹–O–R² structure shows them to be acetals. There are many possible derivatives, but only a few are used with great frequency.

One is methoxymethyl ether (O-CH₂OMe O**MOM**),²⁸ formed by reaction of the alcohol with a base, and then with ClCH₂OCH₃ (chloromethyl methyl ether).²⁹ The MOM group is somewhat sensitive to acid, but is generally stable in the pH 4-12 range. It is important to note that HCl in an aqueous THF solution (pH \approx 1) does not cleave the BnO group, whereas it does cleave the OMOM group. The MOM group is stable to nucleophiles, organometallic reagents, hydrides, catalytic hydrogenation (except with platinum catalysts in acidic media) and to oxidation, but reacts with acidic media to give the alcohol. Sensitivity to acid is the key to removing this group, and both 50% aqueous acetic acid with a sulfuric acid catalyst³⁰ and HCl in MeOH³¹ are commonly used for deprotection. In a synthesis of spiculoic acid A,³² Mehta and Kundu prepared alcohol **38**, and subsequent reaction with MOM chloride gave **39** in 85% yield. Eleven synthetic steps converted **39** to **40**, which incorporated the other alcohol protecting groups *O*-benzyl (see above) and *O*-diphenyl-*tert*-butylsilyl (see sect. 7.3.A.ii). Treatment

^{26.} Reference 2a, pp 26-27, 296-298; Reference 2b, pp 41-42; Reference 2c, pp 65-67; Reference 2d, pp 82-84.

^{27. (}a) Beyerman, H.C.; Bontekoe, J.S. Proc. Chem. Soc. 1961, 249; (b) Beyerman, H.C.; Heiszwolf, G.J. J. Chem. Soc. 1963, 755.

^{28.} Reference 2a, pp 16-17, 296-298; Reference 2b, pp 17-21; Reference 2c, pp 27-33; Reference 2d, pp 30-38.

^{29.} Kluge, A.F.; Untch, K.G.; Fried, J.H. J. Am. Chem. Soc. 1972, 94, 7827.

^{30.} Laforge, F.B. J. Am. Chem. Soc. 1933, 55, 3040.

^{31.} Auerbach, J.; Weinreb, S.M. J. Chem. Soc. Chem. Commun. 1974, 298.

^{32.} Mehta, G.; Kundu, U.K. Org. Lett. 2005, 7, 5569.

with BF₃•etherate in the presence of 1,3-dithiane removed the MOM group to give alcohol **41** in 84% yield.



A variation on the MOM protecting group replaces the oxygen with sulfur to generate the methylthio-methyl ether (O–CH₂SMe, OMTM).³³ The target alcohol is converted to the alkoxide with sodium hydride or another suitable base, and then treated with chloromethylmethyl sulfide (ClCH₂SMe).^{34a} An alternative method uses DMSO and acetic anhydride in acetic acid.^{34b} This thioether protecting group is stable to pH 1-12 but it is sensitive to very strong aqueous acid and to Lewis acids (especially mercuric salts). It reacts with many hydrogenation catalysts (bivalent sulfur is a poison, sec. 4.8.A) and can be oxidized to a sulfoxide with many oxidizing agents (sec. 3.9.A). The group is stable to reaction with nucleophiles, organometallics or hydrides. It can be removed by treatment with Lewis acids, and mercury salts are especially effective.³⁴ This group can also be removed by treatment with iodomethane in mildly basic solution in some cases.³³

The MTM group was used to protect several of the alcohol groups in Corey and co-worker's synthesis of erythronolide A.³⁵ Alcohol **42** contains a sensitive OH group and was converted to the MTM derivative (**43**). This allowed the construction of the *tris*(MTM) lactone **44**. Treatment with potassium carbonate (K_2CO_3) and CH_3I (aq. acetone, 40°C, 15 h) gave the triol (**45**) in 80% yield, which was converted to erythronolide A.



^{33.} Reference 2a, pp 17-18, 296-298; Reference 2b, pp 21; Reference 2c, pp 33-35; Reference 2d, pp 38-41.

^{34. (}a) Corey, E.J.; Bock, M.G. *Tetrahedron Lett.* **1975**, 3269; (b) Pojer, P.M.; Angyal, S.J. *Aust. J. Chem.* **1978**, 31, 1031.

^{35. (}a) Corey, E.J.; Trybulski, E.J.; Melvin, Jr., L.S.; Nicolaou, K.C.; Secrist, J.A.; Lett, R.; Sheldrake, P.W.; Falck, J.R.; Brunelle, D.J.; Haslanger, M.F.; Kim, S.F.; Yoo, S. J. Am. Chem. Soc. 1978, 100, 4618, 4620; (b) Corey, E.J.; Hopkins, P.B.; Kim, S.; Yoo, Y.; Nambiar, K.P.; Falck, J.R. Ibid., 1979, 101, 7131.

Another common acetal protecting group is the 2-methoxyethoxymethyl ether $(-O-CH_2OCH_2CH_2OMe, OMEM)$.³⁶ The MEM group is attached by reaction of the alcohol with NaH in THF or DME (although diisopropylethylamine [Hünig's base] can be used in dichloromethane), and then reaction with methoxyethoxy chloromethyl ether.³⁷ The MEM group is stable to pH 1-12, oxidizing agents, nucleophiles, hydrogenation, hydrides, and organometallics, but is cleaved in strong aqueous acid (pH < 1) and is sensitive to Lewis acids. This latter observation is the key to deprotection. Either zinc bromide (ZnBr₂) or titanium tetrachloride (TiCl₄) in dichloromethane can be used for deprotection,³⁷ although other deprotection methods are known. In a synthesis of ristocetin aglycone, Boger and coworkers converted alcohol **46** to the OMEM derivative **47** in 99% yield.³⁸ After 14 steps, **48** was obtained and treatment with *B*-bromocatecholborane gave **49** in > 90% yield.



A variation of the OMEM group is the 2-(trimethylsilyl)ethoxymethyl ether (O–CH₂OCH₂CH₂– SiMe₃, OSEM),³⁹ developed by Lipshutz and co-workers.⁴⁰ The trimethylsilyl group is used as a trigger for facile deprotection of the alcohol. The OSEM group is attached to an alcohol by reaction with 2-(trimethylsilyl)ethoxymethyl chloride (Me₃SiCH₂CH₂OCH₂Cl) and Hünig's base. The SEM group is stable in a pH range of 4-12. Some nucleophiles and many Lewis acids react with this group, but it is generally stable to hydrides and to many organometallics

^{36.} Reference 2a, pp 19, 296-298; Reference 2b, pp 27-29; Reference 2c, pp 41-44; Reference 2d, pp 49-53.

^{37.} Corey, E.J.; Gras, J.-L.; Ulrich, P.Tetrahedron Lett. 1976, 809.

^{38.} Crowley, B.M.; Mori, Y.; McComas, C.C.; Tang, D.; Boger, D.L. J. Am. Chem. Soc. 2004, 126, 4310.

^{39.} Reference 2a, pp 20-21, 296-298; Reference 2b, pp 30-31; Reference 2c, pp 45-48; Reference 2d, pp 54-58.

^{40. (}a) Lipshutz, B.H.; Pegram, J.J. *Tetrahedron Lett.* **1980**, *21*, 3343; (b) Lipshutz, B.H.; Moretti, R.; Crow, R. *Ibid.*, **1989**, *30*, 15; (c) Lipshutz, B.H.; Miller, T.A. *Ibid.*, **1989**, *30*, 7149.

(such as butyllithium), as well as most oxidizing agents. The presence of silicon makes the group sensitive to fluoride [as with silyl protecting groups, see below], and treatment with tetrabutylammonium fluoride (n-Bu₄N⁺F⁻, TBAF) usually regenerates the alcohol, but not always. Indeed, the OSEM group is difficult to remove in some cases. In the Keaton and Phillip's synthesis of (–)-7-demethylpiericidin A₁,⁴¹ the pyridyl OH unit in **50** was protected as the SEM derivative (**51**) in 97% yield using silver carbonate to effect the coupling. This fragment was modified and then coupled to another fragment in a convergent synthesis to give **52**. Final treatment with tetrabutylammonium fluoride removed the SEM group as well as the cyclic silyloxy unit to give **53** in 70% yield.



Tetrahydropyranyl ethers (OTHP, see 55)⁴² are acetal protecting groups that can be found in many older organic syntheses. An alcohol reacts with dihydropyran (54) in the presence of an acid, such as *p*-toluenesulfonic acid, to give the THP derivative (55) via an oxygen stabilized cation.⁴³ One problem with this protecting group is the fact that a new stereogenic center is created when 55 is formed. If ROH is chiral, 55 will exist as diastereomers, which may make identification, isolation, and purification difficult if this protecting group is carried through many synthetic steps. This group is stable to base (pH 6-12) but unstable to aqueous acid and to Lewis acids.



It is relatively stable to nucleophiles and organometallics. It is also stable to hydrogenation, hydrides, and oxidizing agents.⁴³ It is removed with aqueous acid or methanolic tosic acid.⁴⁴ Greene reported⁴³ that explosions have occurred when tetrahydropyranyl ethers are treated

^{41.} Keaton, K.A.; Phillips, A.J. J. Am. Chem. Soc. 2006, 128, 408.

^{42.} Reference 2a, pp 21-22, 296-298; Reference 2b, pp 31-34; Reference 2c, pp 49-52; Reference 2d, pp 59-68.

^{43.} This report is taken from (a) Bernady, K.F.; Floyd, M.B.; Poletto, J.F.; Weiss, M.J. J. Org. Chem. 1979, 44, 1438;(b) Miyashita, M.; Yoshikoshi, A.; Grieco, P.A. Ibid. 1977, 42, 3772.

^{44.} Corey, E.J.; Niwa, H.; Knolle, J. J. Am. Chem. Soc. 1978, 100, 1942.

with diborane:basic hydrogen peroxide⁴⁵ or with 40% peroxyacetic acid.⁴⁴ An example involving this protecting group is taken from von Zezschwitz and co-worker's synthesis of okaspirodiol.⁴⁶ The initial synthetic steps that incorporated the OTHP unit were taken from earlier work of White and co-workers during their degradation and absolute configurational assignment to C34-botryococcene.⁴⁷ Alkynyl alcohol **56** was protected as the THP derivative **57** in 90% yield. The synthesis of **58** required only two steps, but converged with a fragment that contained a second THP group. Final treatment with methanolic HCl liberated the two hydroxyl groups in **59** (>80% yield), which was used to complete the synthesis.



Greene classified another generic type of acetal protecting group as a substituted ethyl ether. A common member of this group is 1-ethoxyethyl ether [O–CH(OCH₂Me)Me, OEE].⁴⁸ As with the OTHP group, diastereomers can be generated when the OEE group is incorporated in a molecule with the same problems. The protected derivative will exist as diastereomers, since there are two stereogenic centers. The group is usually attached to the alcohol via reaction with ethyl vinyl ether under acid conditions (HCl or tosic acid).⁴⁹ The group is stable to a relatively narrow pH range of 6-12, but it is compatible with reactions of nucleophiles, organometallics, hydrogenation, hydrides, and most oxidants. It is sensitive to acid conditions and to Lewis acids. The most common methods for cleavage to the alcohol are treatment of the OEE ether with aqueous acetic acid,^{49a} or with aqueous HCl in THF.^{49b} Fukuda and Okamoto used this protecting group in a synthesis of AM6898A.⁵⁰

7.3.A.ii. Silyl Ether Protecting Groups. Silyl ethers have become extremely important for the protection of alcohols with the generic structure $OSiR_3$. Variation in the R group leads to significant differences in the stability of the protecting group. In general, silyl ethers can be cleaved with aqueous base or acid, but the rate of hydrolysis for a secondary silyl ether

^{45.} See Meyers, A.I.; Schwartzman, S.; Olson, G.L.; Cheung, H.-C. Tetrahedron Lett. 1976, 2417.

^{46.} Bender, T.; Schuhmann, T.; Magull, J.; Grond, S.; von Zezschwitz, P. J. Org. Chem. 2006, 71, 7125.

^{47.} White, J.D.; Somers, T.C. G. Reddy, N. J. Org. Chem. 1992, 57, 4991.

^{48.} Reference 2a, pp 25, 296-298; Reference 2b, pp 414-415; Reference 2c, pp 709-711; Reference 2d, pp 74-75.

^{49. (}a) Chládek, S.; Smrt, J. Chem. Ind (London) 1964, 1719; (b) Meyers, A.I.; Comins, D.L.; Roland, D.M.; Henning, R.; Shimizu, K. J. Am. Chem. Soc. 1979, 101, 7104.

^{50.} Fukuda, Y.; Okamoto, Y. Tetrahedron 2002, 58, 2513.

is significantly slower than that of a primary silvl ether.⁵¹ In addition, alkyl alcohols are more reactive than phenolic derivatives, and the order of reactivity for other silane-protected functional groups is $COOSiR_3 > NHSiR_3 > CONHSiR_3 > SSiR_3$.⁵² Steric factors play a major role in the relative stability of the OSiR₃ group in cleavage reactions. The prototype of this class of protecting groups is the trimethylsilyl ether [O–Si(Me)₃, OTMS].⁵³ The group is usually attached to the alcohol by reaction with chlorotrimethylsilane (Me₃SiCl) in the presence of an amine base such as triethylamine or pyridine.⁵⁴ although Wuts and Greene list several other methods. This group is sensitive to many aqueous conditions, and the TMS group is sometimes cleaved in an aqueous workup procedure.⁵⁵ The group is not very stable to organometallics such as Grignard reagents, or to nucleophiles, hydrogenation or hydrides, but it can be used with some oxidants. The sensitivity of OTMS to these reagents is often the result of the aqueous or acid workup procedures that are required for a given reaction. If strictly anhydrous conditions are used, the TMS group can be used for short-term protection. Under aprotic conditions, fluoride ion (such as tetrabutylammonium fluoride) readily attacks silicon and cleaves the O-Si bond.^{51a} A synthetic example is the protection of the alcohol moiety in 60, using trimethylsilyl triflate and 2,6-lutidine to give 61 in 86% yield, in Hiersemann and co-worker's synthesis of (-)-15-acetyl-3-propionyl-17-norcharaciol.⁵⁶ This group was sufficiently stable to allow the next three steps to give fragment 62 that also contained *O-tert*butyldimethylsilyl (OTBDMS, see below) and O-triethylsilyl (OTES, see below) protecting groups. Treatment with tetrabutylammonium fluoride removed both the OTMS group and the OTES group to give 63.



^{51. (}a) Reference 2a, pp 39; (b) McInnes, A.G. Can. J. Chem. 1965, 43, 1998.

- 55. Reference 2a, pp 296-298; Reference 2b, pp 414-415; Reference 2c, pp 709-711; Reference 2d, pp 171-178.
- 56. Helmboldt, H.; Kohler, D.; Hiersemann, M. Org. Lett. 2006, 8, 1573.

^{52. (}a) Reference 51a; (b) Cooper, B.E. Chem. Ind. (London) 1978, 794.

^{53.} Reference 2a, pp 40-42; Reference 2b, pp 68-73; Reference 2c, pp 116-121; Reference 2d, pp 171-178.

^{54. (}a) Corey, E.J.; Snider, B.B. J. Am. Chem. Soc. 1972, 94, 2549; (b) Sweely, C.C.; Bentley, R.; Makita, M.; Wells, W.W. Ibid., 1963, 85, 2497.

The fact that hydrolysis of the OTMS group is so facile makes it unsuitable for most alcohol moieties that require long-term protection. A more stable silyl derivative is the triethylsilyl group (O-SiEt₃, OTES).⁵⁷ This group is attached by reaction of the alcohol with chlorotriethylsilane (Et₃SiCl) and pyridine.⁵⁸ The OTES group is generally more stable than OTMS, and in particular it is less sensitive to water. Aqueous acetic acid cleaves OTES and also alcoholic tosic acid,⁵³ but fluoride can also be used for removing it. In a synthesis of (+)-dolastatin 19 by Paterson and co-workers,⁵⁹ fragment **64** was converted to the tetra(triethylsilyloxy) or TES derivative **65**, in 72% yield using triethylsilyl triflate and 2,6-lutidine. After four synthetic steps that included a convergent step, compound **66** was obtained. Treatment with tosic acid in methanol deprotected the OTES alcohol but not the dimethyl-*tert*-butylsilyl alcohol (see below) to give **67** but this diol was not isolated but treated *in situ* with *tert*-butyldimethylsilyl triflate and 2,6-lutidine (see below) to give **68** in 74% yield. Note that treatment with tosic acid liberated the OTES alcohol, but that hydroxyl group reacted with the methanol.



Triisopropylsilyl ether $[O-Si(CH(Me)_2)_3, OTIPS]$,⁶⁰ is prepared via triisopropylchlorosilane (*i*-Pr₃SiCl)⁶¹ and imidazole. The group is stable in the pH 2-14 range and it is generally impervious to nucleophiles, organometallics, hydrogenation (except in acetic acid), hydride and oxidizing agents. It is usually removed with fluoride (TBAF or aqueous HF). In an example

^{57.} Reference 2a, p 44; Reference 2b, pp 72-73; Reference 2c, pp 121-123; 709-711; Reference 2d, pp 178-183.

^{58.} Hart, T.W.; Metcalfe, D.A.; Scheinmann, F. J. Chem. Soc. Chem. Commun. 1979, 156

^{59.} Paterson, I.; Findlay, A.D.; Florence, G. J. Org. Lett. 2006, 8, 2131.

^{60.} Reference 2a, pp 50, 296-298; Reference 2b, pp 74-75; Reference 2c, pp 125-127; 709-711; Reference 2d, pp 183-187.

^{61.} Ogilvie, K.K.; Thompson, E.A.; Quilliam, M.A.; Westmore, J.B. Tetrahedron Lett. 1974, 2865.

taken from the Cook and co-worker's synthesis of (–)-macroine,⁶² the primary alcohol unit in diol **69** was selectively protected with triisopropylsilyl chloride in the presence of 2,6-luitidine to give the OTIPS derivative **70** in 90% yield. Four synthetic steps gave the OTIPS protected intermediate **71** and deprotection of the OTIPS groups with TBAF gave **72** in 86% yield.



One of the most used silvl ether protecting groups is *tert*-butyldimethylsilvl [O-Si(Me)₂t-Bu, abbreviated as OTBDMS although it is commonly abbreviated as OTBS].⁶³ The most common method for attaching this group reacts the alcohol with *tert*-butyldimethylsilvl chloride using imidazole^{64a} or dimethylaminopyridine^{64b} as the base. The analogous silvl triflate (*t*-BuMe₂Si-OSO₂CF₃) is also useful for generating this ether from alcohols, with an amine base.^{64c} The group is stable to base and reasonably stable to acid (pH 4 \rightarrow 12) than the other silvl protecting groups, and also to nucleophiles, organometallics, hydrogenation (except in acidic media), hydrides or oxidizing agents. It can be removed with aqueous acid, but fluoride ion is the most common cleavage method (fluoride (tetrabutylammonium fluoride,⁶⁴ tetrabutylammonium chloride, and KF,⁶⁵ and also aqueous HF⁶⁶). Groth and Kesenheimer used this protecting group in a synthesis of (–)-8-*O*-methyltetrangomycin (MM 47755),⁶⁷ for a key alcohol in **73**. Conversion to the silvl ether by reaction the silvl triflate gave **74** in 96% yield. Nine synthetic steps were required to form **75**, and removal of the TBS group with aqueous HF gave **76** in 49% yield.

^{62.} Liao, X.; Zhou, H.; Yu, J.; Cook, J.M. J. Org. Chem. 2006, 71, 8884.

^{63.} Reference 2a, pp 44-46, 296-298; Reference 2b, pp 77-83; Reference 2c, pp 127-141; 709-711; Reference 2d, pp 189-211.

^{64. (}a) Corey, E.J.; Venkateswarlu, A. J. Am. Chem. Soc. 1972, 94, 6190; (b) Chaudhary, S.K.; Hernandez, O. *Tetrahedron Lett.* 1979, 99; (c) Corey, E.J.; Cho, H.; Rücker, C.; Hua, D.H. *Ibid.*, 1981, 22, 3455.

^{65.} Carpino, L.A.; Sau, A.C. J. Chem. Soc. Chem. Commun. 1979, 514.

^{66.} Newton, R.F.; Reynolds, D.P.; Finch, M.A.W.; Kelly, D.R.; Roberts, S.M. Tetrahedron Lett. 1979, 3981.

^{67.} Kesenheimer, C.; Groth, U. Org. Lett. 2006, 8, 2507.



A protecting group that is used with great regularity is the *tert*-butyldiphenylsilyl group [*O*-SiPh₂C(Me)₃, O**TBDPS**].⁶⁸ Hanessian and Lavallee developed this protecting group when it was discovered that the O-TBDMS group was sensitive to hydrogenation.⁶⁹ The TBDPS group is attached to the alcohol by reaction with *tert*-butyldiphenylsilyl chloride (*t*-BuPh₂SiCl) and imidazole.⁶⁹ It has stability characteristics similar to dimethyl-*tert*-butyl derivatives, but is more stable to Lewis acids. An example is the synthesis of macroviracin A by Takahashi and co-workers,⁷⁰ in which alcohol 77 was converted to TBDPS derivative **78** in 96% yield. The conversion to **79** required several steps, in a convergent synthesis (sec. 10.3.C), and deprotection with TBAF gave **80** in 82% yield.



7.3.A.iii. Ester Protecting Groups. Another class of alcohol protecting groups are the *O*-esters (O-COR), where COR is an acyl group. Ester protecting groups are limited in scope due to their susceptibility to nucleophilic acyl substitution, hydrolysis or reduction. Several esters are commonly used in synthesis, however, including acetates, benzoates or mesitoates. Although many esters may be used in synthesis, this discussion will focus only on the more common derivatives.

^{68.} Reference 2a, pp 47-48, 296-298; Reference 2b, pp 83-84; Reference 2c, pp 141-145; 709-711; Reference 2d, pp 211-215.

^{69.} Hanessian, S.; Lavallee, P. Can. J. Chem. 1975, 53, 2975; (b) Idem Ibid., 1977, 55, 562.

^{70.} Takahashi, S.; Souma, K.; Hashimoto, R.; Koshino, H.; Nakata, T. J. Org. Chem. 2004, 69, 4509.

Acetates $(OAc)^{71}$ are formed by reaction of an alcohol with acetic anhydride or acetyl chloride and pyridine or triethylamine. Acetates are stable to pH from 1 up to 8, ylids and organocuprates, catalytic hydrogenation, borohydrides, Lewis acids or oxidizing agents. Hydrolysis with acid or base (saponification) cleaves the ester to the alcohol and an acid. Reaction with LiAlH₄ reductively cleaves the acetate to the alcohol and ethanol. Acetates have found widespread use in synthesis. In the Sha and co-workers synthesis of the hexahydrobenzofuran subunit of avermectin,⁷² diol **81** was acetylated to give **82** in 81% yield. Subsequent elimination of the tertiary alcohol introduced the alkene unit, and deprotection liberated the alcohol in **83** in 60% and 87% respectively.



Alcohols react with benzoyl chloride (PhCOCl) or benzoic anhydride $[(PhCO)_2O]$, with pyridine or NEt₃, to give the benzoyl derivative (benzoate ester, O**Bz**).⁷³ Benzoates are more stable to hydrolysis than acetates, with a pH stability from pH 1 up to 10-11. Treatment with 10% K₂CO₃ (pH 11), for example, will hydrolyze the O–Bz group. Benzoyl esters are more stable to reactions with nucleophiles such as cyanide and acetate, ylids or organocuprates. Benzoate esters also resist catalytic hydrogenation, and reaction with borohydrides or with oxidizing agents. The group is usually cleaved by basic hydrolysis or by reduction with LiAlH₄.

Three additional protecting groups in this category are the mesitoate ester (OCO-C₆H₂-2,4,6-trimethyl, O**Mes**),⁷⁴ the pivaloyl ester (OCO-*t*-Bu, O**Piv**),^{75,76} and the *para*-methoxybenzoyl ester [OCO-C₆H₄-(4-Me)]. The mesitoate ester is formed by reaction of an alcohol with mesitoyl chloride in the presence of pyridine or triethylamine.⁷⁷ This ester is stable to hydrolysis (pH 1-12), nucleophilic attack, organometallics, catalytic hydrogenation; reaction with boranes, borohydrides, Lewis acids or oxidation. This stability is due to the two ortho methyl groups, which block the acyl carbon to attack. Both LiAlH₄⁷⁴ and concentrated alcoholic potassium

- 75. (a) Reference 2c, pp 170-173; 713-716; (b) Reference 2d, pp 250-254.
- 76. For a synthetic example, taken from a synthesis of elutherobin, see Chen, X.-T.; Bhattacharya, S.K.; Zhou, B.; Gutteridge, C.E.; Pettus, T.R.R.; Danishefsky, S.J. J. Am. Chem. Soc. **1999**, 121, 6563.
- 77. Corey, E.J.; Achiwa, K.; Katzenellenbogen, J.A. J. Am. Chem. Soc. 1969, 91, 4318.

^{71.} Reference 2a, pp 53-55, 300-302; Reference 2b, pp 88-92; Reference 2c, pp 150-160; 713-716; Reference 2d, pp 223-239.

^{72.} Sha, C.-K.; Huang, S.-J.; Zhan, Z.-P. J. Org. Chem. 2002, 67, 831.

^{73.} Reference 2a, pp 61-62, 300-302; Reference 2b, pp 100-103; Reference 2c, pp 173-178; 713-716; Reference 2d, pp 255-262.

^{74.} Reference 2a, pp 63-64, 300-302; Reference 2b, pp 103-104; Reference 2c, pp 178-179; 713-716; Reference 2d, p 263.

tert-butoxide^{78,74} will cleave the group. Cleavage of the C–O bond is occasionally a problem with LiAlH₄.⁷⁹ Similar reactivity is observed with OPiv, but the precursor is pivaloyl chloride, *t*-BuCOCl.

The *p*-methoxybenzoyl group (**OPMB** or sometimes **OMPM** as in **83**)⁸⁰ is a useful protecting group. The precursor to this ester is *p*-methoxybenzoyl chloride. Cleavage of the *p*-methoxybenzyl ether unit is usually accomplished by oxidation with DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). An example is taken from the Perkins and Lister synthesis of dolabriferol,⁸¹ in which alcohol **84** was treated with trichloromethyl imidate (**85**) to give the O-PMB derivative **86**, in 84% yield. Three synthetic steps generated **87**, and deprotection by treatment with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) gave **88**.





7.3.A.iv. Protection of Diols. 1,2-Diols are obviously alcohols, but the vicinal nature of the hydroxyls allows them to be protected as cyclic ketals. When a 1,2-diol such as 2,3-butanediol (**89**) reacts with a ketone such as acetone in the presence of an acid catalyst,

a 1,3-dioxolane (90) is formed. Ketals such as 90 that are derived from acetone are called **acetonides** (isopropylidene ketals).⁸² A 1,3-diol will generate a six-membered ring acetonide, which is a 1,3-dioxane derivative. Common methods for acetonide formation are reaction of the diol with 2-methoxy-1-propene in the presence of an acid such as anhydrous HBr⁸³ or reaction

^{78. (}a) Reference 74; (b) Gassman, P.G.; Schenk, W.N. J. Org. Chem. 1977, 42, 918.

^{79.} For cleavage of esters, see Robins, D.J.; Sakdarat, S. J. Chem. Soc. Perkin Trans. 1 1981, 909.

^{80. (}a) Reference 2c, p 36; (b) Stork, G.; Isobe, M. J. Am. Chem. Soc. 1975, 97, 6260.

^{81.} Lister, T.; Perkins, M.V. Org. Lett. 2006, 8, 1827.

^{82.} Reference 2a, pp 76-78, 304-306; Reference 2b, pp 123-127; Reference 2c, pp 207-215; 717-719; Reference 2d, pp 306-318.

^{83.} Corey, E.J.; Kim, S.; Yoo, S.; Nicolaou, K.C.; Melvin, Jr., L.S.; Brunelle, D.J.; Falck, J.R.; Trybulski, E.J.; Lett, R.; Sheldrake, P.W. J. Am. Chem. Soc. 1978, 100, 4620.

of acetone with an acid catalyst.⁸⁴ The group is stable to base, but not to acid (pH 4 \rightarrow 12). It is stable to nucleophiles, organometallics, catalytic hydrogenation, hydrides, and oxidizing agents. It can be cleaved with aqueous HCl, with acetic acid⁸⁵ or with *p*-toluenesulfonic acid in methanol.⁸⁶ This group has been used extensively in the manipulation of carbohydrates. Acetonides are useful in other synthetic applications, as in the protection of the 1,2-diol unit found in **91**, in Danishefsky and Siegel's synthesis of garsubellin A,⁸⁷ which was converted to **92** by reaction with dimethoxypropane and tosic acid in acetone, as part of This protection step was followed by elaboration of the molecule to **93** in three steps, and deprotection with aqueous perchloric acid gave **94**.



Diols react with other aldehydes or ketones to give a wide array of ketals or acetals. Two of the more common derivatives are benzaldehyde (benzylidene acetals) and cyclohexanone (cyclohexylidene ketals). In an initial study by Lee and co-workers aimed at the synthesis of rolliniastatin 1,⁸⁸ diol **95** was converted to the benzylidene acetal (**96**) with benzaldehyde dimethyl acetal, and then converted to **97** in eight synthetic steps. The diol was deprotected to give **98** using hydrogen with a Pd/C catalyst, via hydrogenolysis of the benzylic position. This route proved to be problematic, however, and another route was used to complete the synthesis.



Wuts and Greene² discuss many other ketal protecting groups that have been used in synthesis,

88. Keum, G.; Hwang, C.H.; Kang, S.B.; Kim, Y.; Lee, E. J. Am. Chem. Soc. 2005, 127, 10396.

^{84. (}a) Schmidt, O.Th. *Methods Carbohydr. Chem.* 1963, 2, 318; (b) de Belder, A.N. *Adv. Carbohydr. Chem.* 1965, 20, 219.

^{85.} Lewbart, M.L.; Schneider, J.J. J. Org. Chem. 1969, 34, 3505.

 ⁽a) Ichihara, A.; Ubukata, M.; Sakamura, S. *Tetrahedron Lett.* 1977, 3473; (b) Kimura, J.; Mitsonobu, O. *Bull. Chem. Soc. Jpn.* 1978, 51, 1903.

^{87.} Siegel, D.R.; Danishefsky, S.J. J. Am. Chem. Soc. 2006, 128, 1048.

but acetonide is probably the most common. Cyclopentylidene or cyclohexylidene⁸⁹ and methylene⁹⁰ have been used, as well as a benzophenone ketal.⁹¹ Discussions of methods for protecting alcohols in this section have been extensive, due to the wide range of alcohol protecting groups. Since the hydroxyl is capable of being transformed into a wide range of other functional groups, its protection is of particular importance. More than one hydroxyl moiety is commonly incorporated into a molecule, so the requirement for several selective protecting groups is obvious. The following sections will deal with protection of the other two key functional groups, the carbonyl group found in ketones and aldehydes and also the nitrogen found in amines.

7.3.B. Protection of Aldehydes and Ketones

As with alcohols, developing methods for the protection of ketones or aldehydes must begin with understanding the interfering portion of these molecules. The main reaction of a carbonyl is nucleophilic acyl addition. The oxygen of the carbonyl can also function as a base in the presence of a suitable acid, leading to oxygen-stabilized carbocations (secs. 2.6.B.i, 12.2.A) and a number of reactions. To protect against these reactions, the electrophilic carbon and the π bond of the carbonyl must be removed by conversion to a new functional group that is easily converted back to the carbonyl. One method is to reduce the C=O unit to an alcohol (see Chap. 4), and then protect the OH unit as described in sec. 7.3.A. When it is appropriate in the synthesis, the alcohol is deprotected, and then oxidized back to the aldehyde or ketone. Such a protocol requires four synthetic steps. When feasible, protection procedures should require only two steps: protection and deprotection. With this limitation in mind, the major method for protecting ketones and aldehydes is conversion to a ketal or acetal, using alcohol or diol reactants. A variation of this reaction uses thiol or dithiol reactants to generate dithioketals or dithioacetals. In both cases, treatment with acid (or Lewis acids with the dithio derivatives) readily converts the ketals or acetals back to the ketone or aldehyde. It is important to note that in previous sections, alcohols were protected as ketals or acetals by reaction with ketones or aldehydes, but in this section the carbonyl group will be protected as the ketal or acetal by reaction with alcohols. The group is the same. The difference is which functional group is the object of attention and isolation.

7.3.B.i. Ketals and Acetals. Ketals and acetals are formed by reaction of the carbonyl with alcohols such as methanol or ethanol under anhydrous conditions, in the presence of an acid catalyst. It is obvious that many alcohols can be used to generate acetals and ketals, but methanol and ethanol are probably the most common ones used. The yields of product with these reagents are high, and the lower molecular weight alcohol by-products are easily removed after deprotection. Another attractive feature of the methoxy unit is that it gives simple singlets

^{89.} Reference 2d, p 318.

^{90.} Reference 2d, pp 300-302.

^{91.} Reference 2d, p 344.

in the ¹H NMR spectrum that usually do not obscure important signals from the remainder of protected substrate. In general, dry HCl (gas), sulfuric acid,⁹² BF₃•OEt₂ or *p*-toluenesulfonic acid (PPTS) are the catalysts of choice. The addition of molecular sieves to adsorb water usually improves the yield of ketal or acetal.⁹³ **Diethyl and dimethyl ketals and acetals** are generally stable in a pH range of ~ 4-12, but they are sensitive to strong aqueous acid and to Lewis acids. They are stable to nucleophiles, organometallics, catalytic hydrogenation, hydrides and most oxidizing agents (they do react with ozone).⁹⁴ Conversion of the ketal or acetal back to the ketone or aldehyde is accomplished by treatment with aqueous acids such as trifluoroacetic acid⁹⁵ or oxalic acid (HOOC–COOH).⁹⁶ A popular alternative for regenerating the carbonyl from a ketal or acetal is transketalization, whereby acetone is added along with PPTS (or another acid catalyst). Acetone generates a new ketal (2,2-dimethoxypropane) in this reaction, liberating the originally protected carbonyl derivative.⁹⁷ Other acetals or ketals can be used as well.

In Kuwahara and co-worker's synthesis of a sesquiterpene isolated from the pheromone gland of a stink bug, *Tynacantha marginata* Dallas,⁹⁸ conjugated aldehyde **99** was treated with methanol in the presence of an acidic resin to give the dimethyl acetal **100**. Under the reaction conditions, the O-EE unit was deprotected to the alcohol. Diethoxy acetals are also quite useful. A synthetic example using an diethyl acetal is taken from Tanino and co-workers synthesis of (–)-coriolin.⁹⁹ Formation of the anion from 2-methylpropanenitrile and reaction with the diethyl acetal of 2-bromoacetaldehyde gave **101**. The nitrile unit was elaborated to the methylthio-ketone unit in **102**, and treatment with sulfuric acid regenerated aldehyde **103**.



The 1,2- and 1,3-diols, which form cyclic ketals or cyclic acetals [1,3-dioxolanes or 1,3-dioxanes

- 92. Cameron A.F.B.; Hunt, J.S.; Oughton, J.F.; Wilkinson, P.A.; Wilson, B.M. J. Chem. Soc. 1953, 3864.
- 93. Roelofsen, D.P.; Wils, E.R.J.; Van Bekkum H. Recl. Trav. Chim. Pays-Bas 1971, 90, 1141.
- 94. Reference 2a, pp 116-120, 312-314; Reference 2b, pp 178-183; Reference 2c, pp 297-304; 725-727; Reference 2d, pp 435-444, 1009-1016.
- 95. Ellison, R.A.; Lukenbach, E.R.; Chiu, C.-W. Tetrahedron Lett. 1975, 499.
- 96. Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J.M. Synthesis 1978, 63.
- 97. Colvin, E.W.; Raphael, R.A.; Roberts, J.S. J. Chem. Soc. Chem. Commun. 1971, 858.
- 98. Kuwahara, S.; Hamade, S.; Leal, W.S.; Ishikawa, J.; Kodama, O. Tetrahedron 2000, 56, 8111.
- 99. Mizuno, H.; Domon, K.; Masuya, K.; Tanino, K.; Kuwajima, I.. J. Org. Chem. 1999, 64, 2648.

as discussed for protection of diol, see above], are particularly important for the protection of aldehydes and ketones. 1,3-Dioxolane derivatives are formed by reaction of the carbonyl with 1,2-ethanediol, and reaction with 1,3-propanediol gives 1,3-dioxanes. Dioxane protected ketones are usually hydrolyzed back to the carbonyl faster than the analogous dioxolane protected derivatives, but dioxolane protected aldehydes are hydrolyzed faster than dioxane protected.¹⁰⁰ Despite this difference in reactivity, dioxolanes appear to be the most commonly used protecting group. A carbonyl group reacts with 1,2-ethanediol (ethylene glycol) and PPTS, BF₃•OEt₂, or oxalic acid to give the ethylenedioxy ketal or acetal (a 1,3-doxolane).¹⁰¹ Reaction of the carbonyl with 1,3-propanediol (propylene glycol) under similar conditions generates the 1,3-dioxane, a **propylenedioxy** ketal or acetal.¹⁰² Cyclic ketals are sensitive to acid and are generally stable to pH 4-12 and to reactions with nucleophiles, organometallics, hydrogenation (except in acetic acid), hydrides and oxidizing agents, but they do react with Lewis acids. The most common method for cleavage of the dioxane or dioxolane derivatives is treatment with aqueous acid, including HCl in THF¹⁰³ and aqueous acetic acid.¹⁰⁴ In a synthesis of securinine by Ailbés, de March and co-worker's,¹⁰⁵ a protected aldehyde was incorporated into Grignard reagent 105, which reacted with the aldehyde unit in 104 to give 106. After four synthetic steps, the dioxolane group in 107 was converted to the aldehyde in 108 with DDQ. Note the use of DDQ as another method for deprotection.¹⁰⁶



^{100. (}a) Newman, M.S.; Harper, R.J. J. Am. Chem. Soc. 1958, 80, 6350; (b) Smith, S.W.; Newman, M.S. Ibid 1968, 90, 1249, 1253.

- 105. Ailbés, R.; Ballbé, M.; Busqué, F.; de March, P.; Elias, L.; Figueredo, M.; Font, J. Org. Lett. 2004, 6, 1813.
- 106. Tanemura, K.; Suzuki, .; Horaguchi, T. J. Chem. Soc. Chem. Connun. 1992, 979.

^{101.} Reference 2a, pp 124-125; Reference 2b, pp 188-195, 185-186; Reference 2c, pp 307-308; 725-727; Reference 2d, pp 454-466.

^{102.} Reference 2a, pp 121-126, 312-314; Reference 2b, pp 188-195, 185-186; Reference 2c, pp 307-308; 725-727; Reference 2d, pp 449-452.

 ^{103. (}a) Grieco, P.A.; Nishizawa, M.; Oguri, T.; Burke, S.D.; Marinovic, N. J. Am. Chem. Soc. 1977, 99, 5773; (b) Grieco, P.A.; Yokoyama, Y.; Withers, G.P.; Okuniewicz, F.J.; Wang, C.-L.J. J. Org. Chem. 1978, 43, 4178.

^{104.} Babler, J.H.; Malek, N.C.; Coghlan, M.J. J. Org. Chem. 1978, 43, 1821.

A variation in ketal protection introduces alkyl substituents on the diol moiety. Barrett and co-workers, for example, used 2,2-dimethyl-1,3-propanediol to protect one of the ketone units of the quinone in **109** (forming **110**), in studies aimed at a synthesis of lactonamycin.¹⁰⁷ Seven synthetic steps led to **111**, and deprotection with aqueous acetic acid regenerated the carbonyl in quinone **112**.



7.3.B.ii. Dithioketals and Dithioacetals. The use of cyclic ketals and acetals in conjunction with acyclic carbonyl derivatives offers some selectivity for protection of more than one carbonyl. Expanding the methodology to include the sulfur analogs [dithioketals and dithioacetals, $R_2C(SR')_2$] gives even more flexibility. Both cyclic and acyclic dithio derivatives are known and used, but cyclic dithioketals and acetals are more common. A ketone or aldehyde reacts with two equivalents of a thiol (mercaptan) and an acid (typically HCl and BF₃).^{108,111a} The main advantage of these groups is their stability to acid. They are stable from pH 1-12 and compatible with nucleophiles, organometallics, hydrides and oxidizing agents, although CrO₃ can oxidize the sulfur.¹⁰⁹ Dithioacetals and ketals are particularly reactive with mercuric and silver salts, and are relatively unreactive with many other Lewis acids.¹⁰² Mercuric chloride under aqueous conditions is the most commonly used method for conversion back to the carbonyl.¹¹⁰ As with the oxygenated analogs, the use of cyclic dithioketals and acetals is very prevalent. Reaction with 1,2-ethanedithiol generates 1,3-dithiolanes, and 1,3-propanedithiol gives 1,3-dithianes.

Boron trifluoride etherate (BF₃•OEt₂) is commonly used as an acid catalyst to form dithianes and dithiolanes from ketones and aldehydes.¹¹¹ These protecting groups are similar in their stability to the acyclic derivatives. Cyclic dithioketal and dithioacetal derivatives are relatively insensitive to acid, showing stability from pH 1-12. They are stable to nucleophiles, organometallics, hydrides and many oxidizing agents.¹⁰⁹ They are subject to hydrogenolysis

^{107.} Henderson, D.A.; Collier, P.N.; Pave, G.; Rzepa, P.; White, A.J.P.; Burrows, J.N.; Barrett, A.G.M. J. Org. Chem. 2006, 71, 2434.

^{108.} Zinner, H. Chem. Ber., 1950, 83, 275.

^{109.} Reference 2a, pp 129-132, 312-314; Reference 2b, pp 198; Reference 2c, pp 333-340; 725-727; Reference 2d, pp 477-500.

^{110.} English, Jr., J.; Griswold, Jr., P.H. J. Am. Chem. Soc. 1945, 67, 2039.

 ⁽a) Fujita, E.; Nagao, Y.; Kanelo, K. Chem. Pharm. Bull. 1978, 26, 3743; (b) Corey, E.J.; Bock, M.G. Tetrahedron Lett. 1975, 2643.

and the bivalent sulfur atoms in dithianes can poison heterogeneous hydrogenation catalysts (sec. 4.8.A). They are also sensitive to strong Lewis acids such as aluminum chloride (AlCl₃) and mercuric salts. This latter reaction is the basis of the most common cleavage reaction, the **Corey-Seebach procedure**.¹¹² Other cleavage reagents include Vedejs' use of boron trifluoride etherate in aqueous THF containing mercuric oxide (HgO),^{103c} *N*-Bromosuccinimide,¹¹³ iodine in DMSO,¹¹⁴ ceric ammonium nitrate [Ce(NH₄)₂(NO₃)₆, **CAN**],¹¹⁵ and iodomethane in aqueous media.¹¹⁶ One of the best cleavage procedures is Corey's use of *N*-chlorosuccinimide and silver nitrate in aqueous acetonitrile.¹¹⁷ There are many synthetic examples that use dithiane or dithiolane protecting groups, in combination with many deprotection protocols. In Kadota, Yamamoto and co-worker's synthesis of gambierol,¹¹⁸ aldehyde **113** was converted to dithiane **114** by reaction with 1,3-propanedithiol and BF₃•etherate. This sequence required relatively short-term protection, and after two synthetic steps that produced **115**, the dithiane group was removed with iodomethane and bicarbonate in aqueous acetonitrile to give **116**.



Other 1,2- and 1,3-dithiols have been used as protecting groups, but those discussed here are the most common. Wuts and Greene² discuss other methods for protection of ketones and aldehydes, including cyanohydrins, hydrazones, oximes, oxazolidines or imidazolidines.¹¹⁹ Most of these are rather specialized and will not be discussed in this general presentation.

- (a) Cain, E.N.; Welling, L.L. Tetrahedron Lett. 1975, 1353; (b) Corey, E.J.; Erickson, B.W. J. Org. Chem. 1971, 36, 3553.
- 114. Chattopadhyaya, J.B.; Rama Rao, A.V. Tetrahedron Lett. 1973, 3735.
- 115. Ho, T.-L.; Ho, H.C.; Wong, C.M. J. Chem. Soc. Chem. Commun. 1972, 791.
- (a) Fétizon, M.; Jurion, M. J. Chem. Soc. Chem. Commun. 1972, 382; (b) Takano, S.; Hatakeyama, S.; Ogasawara, K. Ibid., 1977, 68.
- 117. Corey, E.J.; Erickson, B.W. J. Org. Chem. 1971, 36, 3553.
- 118. Kadota, I.; Takamura, H.; Sato, K.; Ohno, A.; Matsuda, K.; Satake, M.; Yamamoto, Y. J. Am. Chem. Soc. 2003, 125, 11893.
- 119. Reference 2a, pp 141-147, 312-314; Reference 2b, pp 210-223; Reference 2c, pp 348-364; Reference 2d, pp 506-528.

 ⁽a) Seebach, D.; Corey, E.J. J. Org. Chem. 1975, 40, 231; (b) Seebach, D. Synthesis 1969, 17; (c) Vedejs, E.; Fuchs, P.L. J. Org. Chem. 1971, 36, 366.

7.3.C. Protection of Amines

The last major type of functional group to be discussed will be amines. The interfering feature of this group is the lone pair of electrons on nitrogen, which makes the molecule basic and nucleophilic. If the amine reacts with alkyl groups, the electron pair is used to forms a bond to carbon to generate an ammonium salt. Alkylation, basicity or oxidation are not possible for ammonium salts, but they are not often used as protecting groups since these charged species are incompatible with many reactions, and solubility can be a problem. In addition, ammonium salts are good leaving groups for substitution and elimination reactions. A more useful protection method generates a derivative in which the electron pair is completely or partially delocalized, reducing the basicity and nucleophilicity of the nitrogen. The three most common methods of amino group protection involve conversion of primary and secondary amines to a tertiary amine (usually benzyl or trialkylsilyl), conversion to an amide or a carbamate, and to a lesser extent, conversion to specialized sulfonamides.¹²⁰ Only the first two of these methods will be discussed.

7.3.C.i. *N*-Alkyl and *N*-Silyl Protecting Groups. Benzyl (*N*-CH₂Ph, N-Bn)¹²¹ is a common alkyl protecting group for nitrogen. An amine is treated with benzyl chloride or benzyl bromide, usually in the presence of a base such as potassium carbonate (K_2CO_3) or hydroxide.¹²² This group is stable to acid and base (pH 1-12) and to nucleophiles, organometallics, hydrides, but reacts with Lewis acids (as a Lewis base). The N-C bond is subject to hydrogenolysis by catalytic hydrogenation or dissolving metals. Hydrogen and palladium on carbon¹²³ (sec. 4.8.E) or sodium in liquid ammonia¹²⁴ (sec. 4.9.D) are the two most common methods of cleavage. Most of the other *N*-alkyl groups used are less general.¹²⁵

A synthetic example using the *N*-benzyl protecting group is taken from Comins and Kuethe's synthesis of (+)-cannabisativine.¹²⁶ Formation of amide **118** in 82% yield from acid chloride **117**, under basic conditions, used *N*-benzyl 4-hydroxylbutylamine prepared from 4-hydroxylbutylamine and benzyl chloride.¹²⁷ After four synthetic steps, to give **119**, treatment with sodium in ammonia deprotected the *N*-benzyl, the *O*-benzyl, and the *N*-tosyl groups to give **120** [(+)-cannabisativine] in 76% yield. It has also been reported that *N*-benzyl can be removed in the presence of *O*-benzyl by catalytic transfer hydrogenation in the presence of a

^{120.} For a review of nitrogen protecting groups, see Theodoridis, G. Tetrahedron 2000, 56, 2339.

^{121.} Reference 2a, pp 272-273, 332-334; Reference 2b, pp 335-338; Reference 2c, pp 620-621; 745-747; Reference 2d, pp 814-818.

^{122.} Velluz, L.; Amiard, G.; Heymès, R. Bull. Soc. Chim. Fr. 1954, 1012.

^{123.} Hartung, W.H.; Simonoff, R. Org. React. 1953, 7, 263.

^{124.} du Vigneaud, V.; Behrens, O.K. J. Biol. Chem. 1937, 117, 27.

^{125.} Reference 2a, pp 268-275, 332-334; Reference 2b, pp 321-341; Reference 2c, pp 573-586; 619-620; Reference 2d, pp 803-809.

^{126.} Kuethe, J.T.; Comins, D.L. J. Org. Chem. 2004, 69, 5219.

^{127.} Lesher, G.Y.; Surrey, A.R. J. Am. Chem. Soc. 1955, 77, 636.

hydrogen donor, 1,4-cyclohexadiene.¹²⁸



The benzyl protection group can be applied to primary or secondary amines. Scammells and Gathergood incorporated a primary amine precursor in the synthesis of psilocin,¹²⁹ by reaction of tosylate **121** with dibenzylamine to give **122** in 56% yield. The dibenzylated species functions as a primary amine surrogate, where both hydrogens of the nitrogen has been removed. A palladium-catalyzed coupling reaction with aryl iodide **123** (sec. 12.7) gave **124**, and catalytic hydrogenation with a palladium on carbon catalyst removed both benzyl groups to give **125** in 83% yield.



A simple silyl protecting group is trimethylsilyl (*N*-SiMe₃, *N*-TMS), which is formed by reaction of the amine with chlorotrimethylsilane and triethylamine or pyridine. The trimethylsilyl group is sensitive to water or alcohol solvents, and the reaction of Me₃SiNEt₂ and alcohols

^{128.} Bajwa, J.S.; Slade, J.; Repic, O. Tetrahedron Lett. 2000, 41, 6025.

^{129.} Gathergood, N.; Scammells, P.J. Org. Lett. 2003, 5, 921.

gives ROSiMe₃. The *N*-TMS group is therefore used under anhydrous conditions.¹³⁰ In a synthesis of (–)-21-isopentenylpaxilline by Smith and Cui¹³¹ reaction of aniline derivative **126** with MeLi (sec. 8.5) and excess chlorotrimethylsilane gave an 84% yield of **127**, blocking both hydrogens on the primary amine. Alkylation (sec. 8.5) gave **128**, and treatment with ethanolic HCl gave **129** in 82% yield for the last two steps.



7.3.C.ii. *N*-Acyl Protecting Groups. Amides are common protecting groups for amines. *N*-Acetyl is the best known of the amide protecting groups, and *N*-acylamines are known as acetamide derivatives (*N*-COMe, *N*-Ac).¹³² Reaction of acetic anhydride or acetyl chloride with an amine, in the presence of a base such as pyridine or triethylamine will generate the acetamide.¹³³ Acetamides are sensitive to strong acid and base, but are stable in the pH range $1\rightarrow 12$. Nucleophiles and many organometallics react with the *N*-acetyl group. Organolithium reagents are unreactive, although reactive Grignard reagents are. This group can be reduced by catalytic hydrogenation, borane or borohydride reducing agents (not LiAlH₄), and can be oxidized by many oxidizing agents. Reactions that use Lewis acids, such as glycosylation, may cause problems if this protecting group is present. The two major methods for conversion of *N*-acetamides to the amine are treatment with aqueous acid¹³⁴ and treatment with triethyloxonium tetrafluoroborate¹³⁵ (Et₃O⁺BF₄⁻, Meerwein's reagent¹³⁶). Reduction with LiAlH₄ gives the ethylamine derivative, but cleavage is sometimes observed.¹³⁷ In a synthesis of (–)-securinine,¹³⁸ by Honda and co-worker's, the *N*-acetyl group was used to protect **130** as acetamide **131**. Conversion to **132** in five steps was followed by cleavage with trifluoroacetic

134. Dilbeck, G.A.; Field, L.; Gallo, A.A.; Gargiulo, R.J. J. Org. Chem. 1978, 43, 4593.

- 137. Gaylord, N.G. Reductions with Complex Metal Hydrides, Ellis Horwood Ltd., Chichester, 1964, pp 544-546.
- 138. Honda, T.; Namiki, H.; Kaneda, K.; Mizutani, H. Org. Lett. 2004, 6, 87.

^{130. (}a) Reference 2a, pp 283; Reference 2b, pp 69-71; (c) Pratt, J.R.; Massey, W.D.; Pinkerton, F.H.; Thames, S.F. J. Org. Chem. 1975, 40, 1090.

^{131.} Smith III, A.B.; Cui, H. Org. Lett. 2003, 5, 587.

^{132.} Reference 2a, pp 251-252, 328-330; Reference 2b, pp 351-352; Reference 2c, pp 552-555; 741-743; Reference 2d, pp 775-779.

^{133.} Barrett, A.G.M.; Lana, J.C.A. J. Chem. Soc. Chem. Commun. 1978, 471.

^{135.} Hanessian, S. Tetrahedron Lett. 1967, 1549.

 ⁽a) Meerwein, H. Org. Synth. Coll. Vol. 5 1973, 1080; (b) For reactions with amides and lactams see Borch, R.F. Tetrahedron Lett. 1968, 61.

acid to give the amine group in 133.



A simple modification of the structure has dramatic effects on the stability of the protecting group. If trifluoroacetyl is used rather than acetyl, the trifluoroacetamide (*N*-COCF₃, *N*-TFA)¹³⁹ is generated. The trifluoroacetyl group is usually attached by reaction of the amine with trifluoroacetic anhydride [(CF₃CO)₂O] in the presence of triethylamine or pyridine.^{133,140} This group retains its stability to acid, but is more sensitive to base (pH 1-10) than the acetamide analog. It is stable to anhydrous bases or tetraalkylammonium hydroxides. The group reacts with most nucleophiles, organolithium reagents, LiAlH₄ and borohydrides via nucleophilic acyl substitution, but is stable to oxidation, Lewis acids, borane, and most catalytic hydrogenation conditions. It is usually removed with potassium carbonate in aqueous methanol,¹⁴¹ by reduction with sodium borohydride¹⁴² or by ammonia in methanol.¹⁴³ In a synthesis of microsclerodermin E by Ma and Zhu,¹⁴⁴ the primary amine unit in **134** was converted to the trifluoroacetamide (**135**), in 62% yield. After 7 steps, **136** was deprotected with ethanoic sodium borohydride to give a quantitative yield of **137**.



- 139. Reference 2a, pp 254-255, 328-330; Reference 2b, pp 353-354; Reference 2c, pp 556-558; 741-743; Reference 2d, pp 781-783.
- 140. Green, J.F.; Jham, G.N.; Neumeyer, J.L.; Vouros, P. J. Pharm. Sci. 1980, 69, 936.
- 141. (a) Quick, J.; Meltz, C. *Ibid.*, **1979**, *44*, 573; (b) Schwartz, M.A.; Rose, B.F.; Vishnuvajjala, B. J. Am. Chem. Soc. **1973**, *95*, 612.
- 142. Weygand, F.; Frauendorfer, E. Chem. Ber. 1970, 103, 2437.
- 143. Imazawa, M.; Eckstein, F. J. Org. Chem. 1979, 44, 2039.
- 144. Zhu, J.; Ma, D. Angew. Chem. Int. Ed. 2003, 42, 5348.

Benzamides (*N*-COPh, *N*-**Bz**)¹⁴⁵ are formed by reaction of an amine with benzoyl chloride in pyridine or triethylamine.¹⁴⁶ This group is stable to pH 1-14, nucleophiles, organometallics (not RLi), hydrogenation, hydrides (except LiAlH₄, and borane) and oxidizing agents. Cleavage is accomplished with 6 N HCl or HBr in acetic acid,¹⁴⁷ hot and concentrated aqueous NaOH,¹⁴⁸ and reduction with DIBAL-H (sec. 4.6.C).¹⁴⁹

7.3.C.iii. N-Carbamate Protecting Groups. The carbamates (N-COOR) are a related class of protecting groups for nitrogen.¹⁵⁰ Several different carbamates have been used for the protection of amino acids in peptide synthesis. One of the most popular is the *tert*-butyl carbamate (tert-butoxycarbonyl, [NCOC(Me)₃], N-Boc).¹⁵¹ Commercially available BOC-ON® $[(Me)_{3}C-O-CO-CO_{2}N=C(CN)Ph]$ reacts with amines, in the presence of another base such as triethylamine to give the N-Boc derivative.¹⁵² Similarly, reaction with di-tert-butyldicarbonate ([(CH₃)₃CCO]₂CO) under basic conditions gives the BOC-protected amine.¹⁵³ This group is sensitive to strong anhydrous acid (stable to pH $1 \rightarrow 12$) and trimethylsilyl triflate (Me₃Si-OTf), but it is stable to nucleophiles, organometallics (including organolithium reagents although Grignard reagents can react by nucleophilic acyl addition), hydrogenation (except under acidic conditions), hydrides, oxidizing agents (not Jones' conditions), aqueous acid, and mild Lewis acids. The Boc group is usually removed by treatment with aqueous HCl¹⁵⁴ or with anhydrous trifluoroacetic acid.¹⁵⁵ In a synthesis of the C(21)-C(26) fragment of superstolide A by Nishida and co-workers¹⁵⁶ the amide in **138** was converted to the N-Boc derivative **139**, in 98% yield. After six synthetic steps to give 140, treatment with trifluoroacetic acid cleaved the Boc group to give the free amine in 141.



- 145. Reference 2a, pp 261-263, 328-330; Reference 2b, pp 355-356; Reference 2c, pp 560-561; 741-743; Reference 2d, pp 785-787.
- 146. White, E. Org. Synth. Collect. Vol. 5 1973, 336.
- 147. Ben-Ishai, D.; Altman, J.; Peled, N. Tetrahedron 1977, 33, 2715.
- 148. Khorana, H.G.; Turner, A.F.; Vizsolyi, J.P. J. Am. Chem. Soc. 1961, 83, 686.
- 149. Gutzwiller, J.; Uskoković, M. J. Am. Chem. Soc. 1970, 92, 204.
- 150. Reference 2a, pp 222-248, 324-326; Reference 2b, pp 327-330; Reference 2c, pp 518-525; 737-739; Reference 2d, pp 707-718.
- 151. Reference 2a, pp 324-326; Reference 2d, pp 725-735.
- 152. Itoh, M.; Hagiwara, D.; Kamiya, T. Bull. Chem. Soc. Jpn. 1977, 50, 718.
- 153. Tarbell, D.S.; Yamamoto, Y.; Pope, B.M. Proc. Natl. Acad. Sci. 1972, 69, 730.
- 154. Stahl, G.L.; Walter, R.; Smith, C.W. J. Org. Chem. 1978, 43, 2285.
- 155. Lundt, B.F.; Johansen, N.L.; Vølund, A.; Markussen, J. Int. J. Pept. Protein Res. 1973, 12, 258.
- 156. Nagata, T.; Nakagawa, M.; Nishida, A. J. Am. Chem. Soc. 2003, 125, 7484.



Another widely used carbamate is the benzyl carbamate (*N*-CO₂CH₂Ph, *N*-Cbz, benzyloxy carbonyl),¹⁵⁷ which Greene points out has been used since 1932.¹⁵⁸ The group is attached by reaction of an amine with benzyl chloroformate (PhCH₂O₂CCl) in the presence of base (aqueous carbonate or triethylamine). The group is very stable to acid and base (pH 1-12), to nucleophiles, to milder organometallics (it reacts with organolithium reagents and Grignard reagents), to milder Lewis acids, and to most hydrides (it reacts with LiAlH₄). The group is sensitive to hydrogenolysis by catalytic hydrogenation, which is the primary means of cleaving this group (Pd on carbon is the usual catalyst).^{152,159}

In a synthesis of diazonamide A,¹⁶⁰ Nicolaou and co-workers protected amine **142** as the Cbz derivative **143** in 94% yield. This group remained intact through 29 steps, including a convergent synthetic step, until **144** was obtained. Catalytic hydrogenation removed the Cbz group to give **145**, in >80% yield, which was one step away from diazonamide A.



^{157.} Reference 2a, pp 239-241, 324-326; Reference 2b, pp 335-338; Reference 2c, pp 531-537; 737-739; Reference 2d, pp 748-756.

- 159. Meienhofer, J.; Kuromizu, K. Tetrahedron Lett. 1974, 3259.
- 160. Nicolaou, K.C.; Rao, P.B.; Hao, J.; Reddy, M.V.; Rassias, G.; Huang, X.; Chen, D.Y.-K.; Snyder, S.A. *Angew. Chem. Int. Ed.* 2003, 42, 1753.

^{158. (}a) Reference 2a, p239; (b) Bergmann, M.; Zervas, L. Berichte 1932, 65, 1192.

7.4. CONCLUSION

It is obvious that the preceding discussions are not exhaustive, but they are representative of the methods used by synthetic chemists to protect key functional groups. The monographs by Wuts and Greene² also discuss methods for protection of alkynes,¹⁶¹ phosphates,¹⁶² carboxylic acids,¹⁶³ amides¹⁶⁴ and thiols.¹⁶⁵ These monographs also contain detailed discussions of other protecting groups that can be used for alcohols, amines, ketones, and aldehydes.

There are obviously other situations that demand a protecting group, but the cases presented above give a useful arsenal of protecting groups as well as a sample of the situations that require their use. One should always be cautious with protecting groups, remembering that each protection-deprotection sequence adds two steps to a synthesis that diminishes the overall yield. Protecting and deprotecting steps often involve the use of an excess of reagents. These reagents are also often cheap, and the yields are usually high. Also, one-pot and simultaneous deprotection saves steps. New protecting groups for specific and general situations are always being developed, and a search of the current literature is always useful.

With this chapter, the first part of this book is complete. Functional groups have been introduced, and the manipulation and interchange of functional groups and their protection have been discussed. All of the fundamental concepts for organic synthesis have also been introduced: stereochemistry, chirality, conformational control, chelation effects and various problems in selectivity. The remaining chapters will deal with formation of carbon-carbon bonds, but the basic principles introduced in Chapters 1-7 will be invoked throughout.

^{161.} Reference 2d, pp 927-933.

^{162.} Reference 2d, pp 934-985.

^{163.} Reference 2b, pp 224-276; Reference 2c, pp 369-453; 729-731; Reference 2d, pp 533-646.

^{164.} Reference 2a, pp 152-192, 315-317; Reference 2b, pp 349-362; Reference 2c, pp 632-647.

^{165.} Reference 2a, pp 195-222, 319-321; Reference 2b, pp 277-308; Reference 2c, pp 454-493; 733-735; Reference 2d, pp 647-695.

HOMEWORK

1. In each of the following, discuss the relative merits of protecting functional groups or finding a chemoselective reagent for: (i) reduction with hydrides, (ii) oxidation with Jones or PCC, (iii) catalytic hydrogenation, and (iv) reaction with MeMgBr (Chap. 8).



2. In the transformation of **A** to **B**, and then to **C**, taken from the synthesis of 7-deoxypancratistatin, deprotection was followed by conversion of a lactone to a lactam. Provide a mechanism for the deprotection of both the O-MOM group and the dioxolane, giving a triol, and also for the lactone-lactam conversion in the second step.



3. Explain the following transformation.



4. In each of the following, give the major product. Show stereochemistry where it is appropriate.




5. For each of the following, determine if protection is required in the given sequence. If so, choose the protecting group(s), explain your choice(s), and provide all necessary reagents for the entire sequence.





6. In each case, complete the synthesis showing all reagents and all intermediate products.



chapter 8 C^d Disconnect Products: Nucleophilic Species that Form Carbon-Carbon Bonds

8.1. INTRODUCTION

The formation of new carbon-carbon bonds poses a major challenge in a synthesis of a complex molecule. Introduction of new functional groups that are compatible with existing functional groups, and also with the reagents that are necessary to complete the transformation further complicates the problem. Finally, the problems of regioselectivity, stereoselectivity, chemoselectivity, and absolute configuration of the stereogenic centers must be addressed in a reasonable manner. As an introduction, the major reactions that build new carbon-carbon bonds have been classified into four major types: nucleophilic, electrophilic, pericyclic and radical reactions. This chapter will focus on those reactions that employ a nucleophilic carbon species. Referring back to Chapter 1, disconnection of a bond generated two fragments (R-C^a and R-C^d), where R-C^d was a donor or nucleophilic fragment and R-C^a was an acceptor or electrophilic fragment (sec. 1.2). The main purpose of this chapter is to identify those types of molecules that function as C^d, and to expand on the number of reactions that were presented in Chapter 1. In most cases the nucleophilic carbon is an organometallic derivative, where the metal is magnesium, lithium, sodium, potassium or a transition metal.

8.2. CYANIDE

8.2.A. Formation of Nitriles

Cyanide ion is a powerful nucleophile that offers a simple but convenient method for generating carbon-carbon bonds. When cyanide displaces a leaving group in a $S_N 2$ reaction, the carbon chain is extended by one carbon, and the nitrile can be converted to a variety of other functional groups.¹

$$R \rightarrow X + NaCN \rightarrow R \rightarrow C \equiv N + NaX \qquad X = Br, Cl, I, OSO_2R$$

Williamson reported the displacement reaction of ethyl halides or sulfonate esters by cyanide ion to give propanenitrile (CH₃CH₂CH₂CN)¹ in 1854,² but Wöhler and Liebig synthesized the

^{1.} Mowry, D.T. Chem. Rev. 1948, 42, 189.

^{2.} Williamson, A.E. J. Prakt. Chem. 1854, 61, 60.

first nitrile in 1832.³ Since the reaction with an alkyl halide is an $S_N 2$ process (sec. 2.6.A.i), the best yields of nitrile are obtained with primary and secondary substrates, whereas tertiary halides such as 2-chloro-2-methylbutane sometimes react via elimination to give the alkene (sec. 2.9.A).⁴ Cyanide displacement of secondary halides often gives poor yields, however. The use of polar, aprotic solvents such as DMSO, DMF or THF give the best yields of nitriles such as hexanenitrile (capronitrile, 97% yield after 20 minutes (sec. 2.6.A.i).

Sulfonate ester leaving groups can also be used, as in the conversion of alcohol 1 to the mesylate group and then to nitrile 2 with NaCN in DMSO,⁵ in a synthesis of dipeptide nitriles as reversible and potent cathepsin S inhibitors by Ward, Spero and co-workers. The S_N2 reactions proceed with the expected inversion of configuration. Another common reagent that generates a nitrile is tosylmethylisocyanide (TsCH₂N=C, also called TosMIC),⁶ which reacts with ketones or aldehydes to generate a nitrile ($R_2C=O \rightarrow R_2CH-C=N$).⁶



Reactions that incorporate a cyano group add one carbon to that molecule. Nitriles are versatile synthetic intermediates since they can be converted to several other functional groups. Three important reactions of nitriles are hydrolysis to acid derivatives,⁷ reduction to amines (secs. 4.2.C.iii, 4.8.D), and reduction to aldehydes⁸ (secs. 4.3, 4.6.C, 4.9.H). In this chapter, we will see that nitriles react with both Grignard reagents (sec. 8.4.C.iii) and organolithium reagents (sec. 8.5.E) to form ketones. Treatment of nitriles containing an α -proton with a strong base, such as lithium diisopropylamide, generates the α -carbanion, which can react with alkyl halides, aldehydes, or ketones or another nitrile (see the Thorpe reaction in sec. 9.4.B.iv). Reactions of cyanide are not limited to alkylation of halides and sulfonate esters. Epoxides are also opened at the less sterically hindered carbon by cyanide via an S_N2-like process.⁹

Disconnection of a C–CN bond is particularly attractive when the CN unit is attached to a primary or a secondary carbon, which reflects the relative ease of formation of this bond by the

^{3.} Wöhler, F.; Liebig, J. Annalen 1832, 3, 249, 267.

^{4.} Hass, H.B.; Marshall, J.R. Ind. Eng. Chem. 1931, 23, 352.

Ward, Y.D.; Thomson, D.S.; Frye, L.L.; Cywin, C.L.; Morwick, T.; Emmanuel, M.J.; Zindell, R.; McNeil, D.; Bekkali, Y.; Givadot, M.; Hrapchak, M.; DeTuri, M.; Crane, K.; White, D.; Pav, S.; Wang, Y.; Hao, M.-H.; Grygon, C.A.; Labadia, M.E.; Freeman, D.M.; Davidson, W.; Hopkins, J.L.; Brown, M.L.; Spero, D.M. J. Med. Chem. 2002, 45, 5471.

^{6.} Oldenziel, O.H.; van Leusen, D.; van Leusen, A.M. J. Org. Chem. 1977, 42, 3114.

For an example taken from a synthesis of *R*-(+)-myrmicarin 217, see Sayah, B.; Pelloux-Léon, N.; Vallée, Y. J. Org. Chem. 2000, 65, 2824.

^{8.} For an example taken from a synthesis of laulimalide, see Mulzer, J.; Hanbauer, M. *Tetrahedron Lett.* 2000, *41*, 33.

^{9.} Kergomard, A.; Veschambre, H. Tetrahedron Lett. 1976, 4069.

 $S_N 2$ reaction and the variety of functional group transformations available. The disconnection for nitriles can be simplified as:

$$R - C = N \implies R - X$$

8.2.B. Isonitriles: Formation and Reactions

Both potassium and sodium cyanide react with alkyl halides to give excellent yields of the nitrile in the solvent DMSO. An isomeric product is often observed (an isonitrile, also called an isocyanide, 4^{10} when the reaction is done in a refluxing alcohol solvent, or when certain metal cyanides are used. Gautier and Hofmann were the first to report isonitriles.¹¹ Cyanide is a bidentate nucleophile, and in general C⁻ is a better nucleophile than N⁻. Nucleophilic strength depends on the metal counterion, however. If M⁺ in MCN is sodium or potassium, which favor formation of ionic compounds, cyanide reacts primarily at carbon. If M⁺ is a metal such as silver that forms relatively covalent bonds, nucleophilic strength at carbon is diminished and cyanide reacts primarily at nitrogen. These competing pathways are illustrated by the reaction of MCN with 1-bromopentane to give 3 or 4. Reaction with potassium cyanide (KCN) generates hexanenitrile (3), whereas reaction with silver cyanide (AgCN) gives the isomeric isonitrile 4. If the reaction is done in alcoholic solvents, which minimizes the nucleophilicity of ionic species, the yield of isonitrile is improved. Table 8.1.1 shows the relationship between formation of isonitriles when ionic and covalent metal cyanides react with alkyl halides. The best yields of isonitrile are observed with silver cyanide and copper cyanide, which form highly covalent metal cyanides. The observed reactivity is due, in part, to the formation and stability of intermediates such as 5. Reaction of an alkyl halide with silver cyanide is a preparative route to isonitriles, 6, but they can also be formed by dehydration of formamide derivatives.¹²

 ⁽a) Guillemard, H. Compt. Rend. 1906, 143, 1158; (b) Guillemard, H. Ibid. 1907, 144, 141; (c) Guillemard, H. Ibid. 1907, 144, 326; (d) Guillemard, H. Bull. Soc. Chim. Fr. 1907, 1, 269; (e) Guillemard, H. Ibid. 1907, 1, 530.

^{11. (}a) Gautier, A. Ann. Chim. Paris 1869, 17, 103; (b) Gautier, A. Annalen 1867, 142, 289; (c) Hofmann, A.W. Ibid. 1867, 144, 114.

^{12.} Ugi, I. Isonitrile Chemistry, Academic Press, New York, 1971.

56 11

8 2.6

trace

Table 8.1. Preparation of isonitriles from	alkyl halides and	metal cyanides.
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CuCN

Cd(CN)₂ Ni(CN)₂

Zn(CN)₂ KCN

Hydrolysis of isonitriles with cold, dilute aqueous acid leads to an amine and formic acid. If
the reaction of cyanide with an alkyl halide gives a mixture of nitrile and isocyanide, mild
hydrolysis with aqueous acid affects only the isocyanide, allowing isolation of the nitrile.
Isocyanides can also be converted to the nitrile by thermal rearrangement, but the reaction
requires temperatures of between 140° and 240°C. ¹ Heating 3-α-isocyanocholestane 7 to
270°C, for example, gave 3- α -cyano-cholestane (8). Interestingly, the reaction proceeded with
>99% retention of configuration. ¹³ If the isonitrile does not contain functionality that would
be damaged by heating, good yields of the nitrile can be obtained. Isonitriles are also formed
by formylation of a primary amine followed by dehydration, as in the conversion of 9 to 10 in
a synthesis of kalihinol C (10) by Wood and co-workers. ¹⁴ Note that isocyanates ¹⁵ are easily
formed from isonitriles by reaction with halogens. ^{15b}



^{13.} Horobin, R.W.; Khan, N.R.; McKenna, J.; Hutley, B.G. Tetrahedron Lett. 1966, 5087.

^{14.} White, R.D.; Keaney, G.F.; Slown, C.D.; Wood, J.L. *Org. Lett.* **2004**, *6*, 1123. For another example using this approach, in a synthesis of aspidophytine, see Sumi, S.; Matsumoto, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 1891.

^{15. (}a) Nef, J.U. Annalen 1892, 270, 267; (b) Johnson, Jr., H.W.; Daughhetee, Jr., P.H. J. Org. Chem. 1964, 29, 246.

Isonitriles can be used for a few useful synthetic transformations.^{10,16} The **Passerini reaction**¹⁷ is a convenient route to amide esters and is considered to be a **three-component coupling reaction**.^{18a} When propionic acid was heated with acetone and *tert*-butylisonitrile, for example, the product was α -propanoyloxy amide 11.^{17a} A useful modification of the Passerini reaction used trifluoroacetic acid rather than a normal aliphatic carboxylic acid. When α -phenoxyacetaldehyde (12) reacted with *tert*-butylisonitrile and trifluoroacetic acid (TFA), 13 was formed. Hydrolysis of this trifluoroacetyl ester with aqueous sodium carbonate led to isolation of the α -hydroxyamide (14) in 69% yield.¹⁹ This modification has the advantage that hydrolysis conditions for trifluoroacetate esters are milder than for normal esters. Note that the four-component coupling of an isonitrile, an amine, an acid and an aldehyde or ketone to generate an amido amide is called the Ugi reaction.^{18b-d}



Isonitriles are somewhat limited in their synthetic utility, but they have some interesting disconnections:

$$\mathbb{R} \xrightarrow{O} \mathbb{R}^{1} \mathbb{N} \mathbb{H} \mathbb{R}^{3} \xrightarrow{R} \mathbb{R}^{O_{2}\mathbb{H}} + \mathbb{R}^{3} \mathbb{N} = \mathbb{C} \xrightarrow{R} \mathbb{R}^{2} \mathbb{N} = \overline{\mathbb{C}} \xrightarrow{R}^{3} \mathbb{N} = \overline{\mathbb{C}} \xrightarrow{R} \mathbb{R}^{3} \mathbb{N} = \overline{\mathbb{C}} \xrightarrow{R} \mathbb{N}$$

^{16. (}a) Ferosie, I. Aldrichimica Acta 1971, 4, 21; (b) Dömling, A.; Ugi, I. Angew. Chem. Int. Ed. 2000, 39, 3168.

 ⁽a) Passerini, M. Gazz. Chim. Ital. 1921, 51 II, 126; (b) Passerini, M. Ibid. 1924, 54, 529; (c) The Merck Index, 14th Ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-69; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 482-483.

 ⁽a) For a review, of isocyanide based multi-component coupling reactions, see Dömling, A. Chem. Rev. 2006, 106, 17. For information concerning the Ugi reaction, see (b) Lindhorst, T.; Bock, H.; Ugi, I. Tetrahedron 1999, 55, 7411; (c) Dömling, A.; Ugi, I. Angew. Chem. Int. Ed. 2000, 39, 3168. See pp 3183-3184 and references therein. Also see(d) Tye, H.; Whittaker, M. Org. Biomol. Chem. 2004, 2, 813.

^{19.} Lumma, Jr., W.C. J. Org. Chem. 1981, 46, 3668.

8.2.C. Other Nitrile-Forming Reactions

Aryl halides are inert to reaction with cyanide ion under normal $S_N 2$ conditions (chap. 2, sec. 2.11), but they do react when heated with cuprous salts like cuprous cyanide (CuCN).²⁰ This transformation is called the **Rosenmund-von Braun reaction**,²¹ and it can be applied to a wide range of aryl halides, and the products can subsequently be used in a variety of reactions.²² This transformation does *not* work when potassium or sodium cyanide is used. An amine base such as *N*-methylpyrrolidine is often added to facilitate the reaction. A synthetic example is taken from a synthesis of stachybotrylactam by Kende and co-workers,²³ in which aryl bromide **15** was treated with cuprous cyanide in hot DMF to give a 92% yield of aryl nitrile **16**.



Aliphatic or aromatic carboxylate salts are also nitrile precursors. For example, fusion (250-300°C) of sodium propionate with cyanogen bromide²⁴ gave propanenitrile.^{25,24b} Cyanide is a nucleophile that reacts with carbonyl derivatives via acyl addition, although this is usually a reversible reaction. The classical **Strecker synthesis**^{1,26} used to prepare racemic α -amino acids is based on controlled addition to give a cyanohydrin [RCHCN(OH)]. When phenylacetaldehyde (17) was treated with NH₃ and HCN, for example, the product was the amino nitrile, **18**. Hydrolysis of the nitrile generated the amino acid, phenylalanine (19).²⁶

$$\begin{array}{cccc} Ph & CHO & \xrightarrow{NH_3, HCN} & Ph & \xrightarrow{C=N} & \xrightarrow{H_3O^+} & Ph & \xrightarrow{CO_2} \\ 17 & 18 & 19 \end{array}$$

There are many modifications of the Strecker synthesis, including those by Erlenmeyer, Tiemann, Zelinsky and Stadnikoff or Knoevenagel and Bucherer.¹ In all cases, the reaction produces

^{20.} Newman, M.S.; Boden, H. J. Org. Chem. 1961, 26, 2525.

 ⁽a) Rosenmund, K.W.; Struck, E. *Berichte* 1916, 52, 1749; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-81.

 ⁽a) Ito, T.; Watanabe, K. Bull. Chem. Soc. Jpn. 1968, 41, 419; (b) Akanuma, K.; Amamiya, H.; Hayashi, T.; Watanabe, K.; Hata, K. Nippon Kagakai Zashi 1960, 81, 333 [Chem. Abstr. 56: 406i 1962)]; (c) Cohen, T.; Lewin, A.H. J. Amer. Chem. Soc. 1966, 88, 4521.

^{23.} Kende, A.S.; Deng, W.-P.; Zhong, M.; Guo, X.-C. Org. Lett. 2003, 5, 1785.

 ⁽a) Douglas, D.E.; Eccles, J.; Almond, A.E. Can. J. Chem. 1953, 31, 1127; (b) Douglas, D.E.; Burditt, A.M. Ibid. 1958, 36, 1256; (c) Barltrop, J.A.; Day, A.C.; Bigley, D.B. J. Chem. Soc. 1961, 3185.

^{25.} Payot, P.H.; Dauben, W.G.; Replogle, L. J. Am. Chem. Soc. 1957, 79, 4136.

 ⁽a) Strecker, A. Annalen 1850, 75, 27; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-90; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 632-633.

racemic amino acids but newer methodology introduces enantioselectivity into the process. One modification of the original Strecker procedure uses a chiral amine to produce amino acids with good asymmetric induction.²⁷ Another example of a stereoselective Strecker reaction uses (*R*)-phenylglycinol as chiral auxiliary for the diastereoselective synthesis of (*R*)-amino acids.²⁸ In one example by Irie and co-workers, taken from a synthesis of 8-octylbenzolactam-V9, a selective activator for protein kinase C ϵ and η , aldehyde **20** (containing the chiral auxiliary on nitrogen) reacted with phenylglycinol and trimethylsilyl cyanide to give **21**, in >70% yield after refluxing in methanol.²⁹ Catalytic enantioselective Strecker reactions are also known.³⁰



Other acid derivatives can also be prepared with HCN and carbonyl derivatives. Addition of HCN to a ketone or aldehyde gives a cyanohydrin in a reversible reaction, and hydrolysis gives the α -hydroxy acid.^{1,31} This process is an equilibrium process favoring the cyanohydrin for aliphatic aldehydes and ketones. The yields are usually poor with aryl and diaryl ketones, however. These reactions add the following disconnections to those previously shown for nitriles:

$$Ar - C = N \quad \square \qquad Ar - X \qquad R \stackrel{R^{1}}{\underset{CO_{2}H}{+}} \stackrel{O}{\underset{R}{+}} \stackrel{O}{\underset{R}{+}} \stackrel{O}{\underset{R^{1}}{+}} \qquad R^{2} \stackrel{R^{1}}{\underset{NR_{2}}{+}} \stackrel{CO_{2}R}{\underset{NR_{2}}{+}} \stackrel{R^{1}}{\underset{NR_{2}}{+}} \stackrel{C=N}{\underset{R^{2}}{+}} \stackrel{O}{\underset{R^{2}}{+}} \stackrel{C}{\underset{R^{2}}{+}} \stackrel{O}{\underset{R^{2}}{+}} \stackrel{R^{1}}{\underset{R^{2}}{+}} \stackrel{CO_{2}R}{\underset{R^{2}}{+}} \stackrel{R^{1}}{\underset{R^{2}}{+}} \stackrel{C=N}{\underset{R^{2}}{+}} \stackrel{O}{\underset{R^{2}}{+}} \stackrel{C}{\underset{R^{2}}{+}} \stackrel{C}{\underset{R^{2}}{+} \stackrel{C}{\underset{R^{2}}{+}} \stackrel{C}{\underset{R^{2}}{+}} \stackrel{C}{\underset{R^{2}}{+} \stackrel{C}{\underset{R^{2}}{+}} \stackrel{C}{\underset{R^{2}}{+} \stackrel{C}{\underset{R^{2}}{+}$$

8.3. ALKYNE ANIONS (R-C=C:⁻)

The conjugate base of an alkyne is an alkyne anion (older literature refers to them as acetylides), and it is generated by reaction with a strong base and is a carbanion. It functions as a nucleophile (a source of nucleophilic carbon) in S_N2 reactions with halides and sulfonate esters. Acetylides react with ketones, with aldehydes via nucleophilic acyl addition and with acid derivatives via nucleophilic acyl substitution. Acetylides are important carbanion synthons for the creation of

^{27.} Weinges, K.; Stemmle, B. Chem. Ber. 1973, 106, 2291.

 ⁽a) Chakraborty, T.K.; Hussain, K.A.; Reddy, G.V. *Tetrahedron* 1995, 51, 9179. Also see (b) Ma, D.; Tian, H.; Zou, G. J. Org. Chem. 1999, 64, 120; (c) Ferraris, D.; Young, B.; Cox, C.; Dudding, T.; Drury III, W.J.; Ryzhkov, L.; Taggi, A.E.; Lectka, T. J. Am. Chem. Soc. 2002, 124, 67; (d) Kobayashi, S.; Ishitani, H. Chem. Rev. 1999, 99, 1069; (e) France, S.; Guerin, D.J.; Miller, S.J.; Lectka, T. Chem. Rev. 2003, 103, 2985.

^{29.} Nakagawa, Y.; Irie, K.; Yanagita, R.C.; Ohigashi, H.; Tsuda, K-i.; Kashiwagi, K.; Saito, N. J. Med. Chem. 2006, 49, 2681.

^{30.} For a review, see Groger, H. Chem. Rev. 2003, 103, 2795.

^{31.} Reference 1, pp 231-246.

new carbon-carbon bonds. Some of the chemistry presented here will deal with the synthesis of alkynes (see Chapter 2) in order to provide continuity with the discussion of acetylides.

8.3.A. Preparation of Alkynes

Alkynes have been thoroughly studied over many years³² and numerous methods are available for their preparation.³³ One of the most useful is dehydrohalogenation of dihalides. This method works best for aryl derivatives when trans elimination is possible.³⁴ Treatment of tetrabromide **22** with potassium *tert*-butoxide gave the usual E2 elimination (sec. 2.9.A) to give **23**. Subsequent base induced dehydrohalogenation gave mono-alkyne **24**, since only one trans elimination was possible.³⁵ Treatment of **24** with a second equivalent of base gave bis(alkyne) **25**, but required a cis elimination pathway. This second elimination was more difficult, requiring excess base and more vigorous conditions.



As the chain length of the vinyl halide increases, the yield of terminal alkyne product generally decreases.^{23,36} Vinyl bromide **26** (n = 0) gave 61% of alkyne **27** (n = 0), for example, but 1-bromo-1-hexene (**26**, n = 4) gave only 18% of the corresponding alkyne (**27**, n = 4).³⁶ Alkynes can also be formed from non-terminal (internal) vinyl halides (such as 3-bromo-3-heptene), but when alkoxide bases are used, the vigorous conditions usually required for elimination of the halogen can cause the triple bond of the product to migrate to the terminal position.³⁷

$$\begin{array}{c} H(CH_2)_n \underset{H}{C} = CHBr & \xrightarrow{NaOEt, EtOH} & H(CH_2)_n \xrightarrow{maOEt, EtOH} \\ \hline 26 & 100^{\circ}C & 27 \end{array}$$

1,1-Dibromoalkenes are a useful source of terminal alkynes, which give an alkyne anion when treated with *n*-butyllithium. In a synthesis of (+)-phomactin A by Halcomb and Mohr,³⁸ the **Corey-Fuchs procedure**,³⁹ which is related to the Wittig olefination reaction (see sec. 8.8.A), was used to convert aldehyde **28** to **29**. Subsequent treatment with butyllithium gave **30**, in 92% overall yield.

^{32.} Viehe, H.R. (Ed.) Chemistry of Acetylenes, Marcel Dekker, New York, 1969.

^{33.} Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 569-581.

^{34. (}a) Reference 32, pp 100-168; (b) Fiesselmann, H.; Sasse, K. Chem. Ber. 1956, 89, 1775.

^{35.} Gaudemar-Bardone, F. Ann. Chim. (Paris) 1958, 3, 52.

^{36.} Loevenich, J.; Losen, J.; Dierichs, A. Berichte 1927, 60, 950.

^{37.} Vaughn, T.H. J. Am. Chem. Soc. 1933, 55, 3453.

^{38.} Mohr, P.J.; Halcomb, R.L. J. Am. Chem. Soc. 2003, 125, 1712.

^{39.} Corey, E.J.; Fuchs, P.L. Tetrahedron Lett. 1972, 13, 3769.

TBDPSO

$$H$$
 \xrightarrow{O} Zn $TBDPSO$ H Br $\xrightarrow{O^{\circ}C}$ $TBDPSO$ H Br $\xrightarrow{O^{\circ}C}$ $BuLi, ether$ 30

Coupling is an important reaction of alkynes that leads to di-ynes. Two classical alkynecoupling reactions involve copper derivatives, but a variety of conditions can be used.⁴⁰ In the **Glaser reaction**,⁴¹ an alkyne such as phenylacetylene reacts with basic cupric chloride (CuCl₂), and subsequent air oxidation gives a diyne (in this case **31**, in 90% yield). This reaction has also been reported to give a quantitative yield of **31** in the presence of CuCl₂ and NaOAc, using supercritical CO₂ as the solvent.⁴² Glaser-type coupling of alkynes can be accomplished with copper derivatives and bases other than hydroxide. Cupric acetate and pyridine is also an effective reagent.⁴³ The second important reaction is the **Cadiot-Chodkiewicz coupling**,⁴⁴ in which a bromoalkyne such as reacts with a monoalkyne in the presence of cupric chloride and an amine to give the diyne.^{44a} In a synthesis of panaxytriol by Danishefsky and Yun,⁴⁵ Cadiot-Chodkiewicz cross-coupling of bromo-alkyne **32** and alkyne **33** gave a 63% yield of diyne **34**. Internal coupling reactions are also possible. Indium metal⁴⁶ was used to couple alkynes with allyl bromide with an anti-Markovnikov regiochemistry.

$$Ph \longrightarrow H \xrightarrow{1. CuCl_2, NH_4OH} Ph \longrightarrow Ph \longrightarrow Ph$$

$$31$$

$$HO \longrightarrow Br + \longrightarrow OH \xrightarrow{C_7H_{15}} OH \xrightarrow{CuCl, EtNH_2, 0^{\circ}C} HO \longrightarrow 34$$

$$34 HO \longrightarrow OH$$

- 42. Li, J.; Jiang, H. Chem. Commun. 1999, 2369.
- 43. Brown, A.B.; Whitlock, Jr., H.W. J. Am. Chem. Soc. 1989, 111, 3640.
- (a) Chodkiewicz, W.; Cadiot, P. Compt. Rend. 1955, 241, 1055; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 128-129.
- 45. Yun, H.; Danishefsky, S.J. J. Org. Chem. 2003, 68, 4519.
- (a) Araki, S.; Imai, A.; Shimizu, M.; Yamada, A.; Mori, Y.; Butsugan, Y. J. Org. Chem. 1995, 60, 1841; (b) Ranu, B.C. Eur. J. Org. Chem. 2000, 2347.

^{40.} Cadiot, P.; Chodkiewicz, W. in *Chemistry of Acetylenes*, Viehe, H.G. (Ed.), Marcel-Dekker, New York, *1969*, pp 597-648.

 ⁽a) Glaser, C. Berichte 1869, 2, 422; (b) Idem Annalen 1870, 154, 137; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-37; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 276-277.

8.3.B. Acidity of Terminal Alkynes

Acetylene and other terminal alkynes have an acidic hydrogen atom (C=C-H), and they are weak acids. A strong base is required to remove that proton to give an alkyne anion such as **35**, and this carbanion is a carbon nucleophile that reacts with alkyl halides or sulfonate esters (R¹-X where R¹ = Me, 1°, 2° alkyl, and X = halogen or OSO₂R) via an S_N2 sequence to give disubstituted alkynes such as **36**. In a synthesis of (–)-neodysiherbaine A⁴⁷ by Hatakeyama and co-workers, triflate **37** was treated with the alkyne anion from butyllithium/HC=CCH₂OPMB to give a 96% yield of **38**.



As shown in Table 8.2,⁴⁸ the acidity of a proton is enhanced (lower pK_a) as the **s character** of the carbon to which it is attached increases.⁴⁹ A variety of bases (sodium hydride, lithium, sodium, or potassium amide, lithium dialkyl amides, organolithium reagents or Grignard reagents) can be used to generate an alkyne anion.⁵⁰ 1-Octyne reacted with methylmagnesium bromide, for example, to give methane and the magnesium salt of the acetylide.⁵⁰ This reaction must be considered if a Grignard reaction (secs. 8.4.A, 8.4.F.i) is one step of a planned synthesis that involves a molecule containing a terminal alkyne.⁵¹

^{47.} Takahashi, K.; Matsumura, T.; Corbin, G.R.; Corbin, R.M.; Ishihara, J.; Hatakeyama, S. J. Org. Chem. 2006, 71, 4227.

 ⁽a) Hopkinson, A.C. in *The Chemistry of the Carbon-Carbon Triple Bond*, Patai, S. (Ed. John Wiley, Chichester-New York, *1978*, pp 75-136; (b) Matthews, W.S.; Bares, J.E.; Bartmess, J.E.; Bordwell, F.G.; Cornforth, F.J.; Drucker, G.E.; Margolin, Z.; McCallum, R.J.; McCollum, G.J.; Vanier, N.R. *J. Am. Chem. Soc. 1975*, *97*, 7006; (c) McEwen, W.K. *Ibid. 1936*, *58*, 1124; (d) Streitwieser, Jr., A.; Reuben, D.M.E. *Ibid. 1971*, *93*, 1794.

 ⁽a) Cram. D. Fundamentals of Carbanion Chemistry, Academic Press, New York, 1965; (b) Maksić, Z.B.; Eckert-Maksić, M. Tetrahedron 1969, 25, 5113; (c) Maksić, Z.B.; Randic, M. J. Am. Chem. Soc. 1973, 95, 6522; (d) Emsley, J.W.; Feenez, J.; Sutcliffe, C.H. High Resolution NMR, Pergamon Press, New York, 1966.

^{50.} Kriz, J.; Beneš, M.J.; Peška, J. Tetrahedron Lett. 1965, 2881.

^{51. (}a) Prevost, C.; Gaudemar, M.; Honigberg, J. *Compt. Rend.* **1950**, 230, 1186; (b) Wotiz, J.H.; Matthews, J.S.; Lieb, J.A. *J. Am. Chem. Soc.* **1951**, 73, 5503.

Table 0.2. Relative Acture of Common Weak Actus

<u>Acid</u>	<u>Conjugate Base</u>	<u>pK</u> a
RC=CH	RC=C:	25
R ₂ C=CH ₂	R ₂ CH3=CH:	36
0	0	
H ₃ C [▲] CH ₃	$H_3C \ CH_2$	19
ROH	RO	17

The acidity of an alkynyl hydrogen is strongly influenced by the nature of the group on the other side of the triple bond, as shown in Table 8.3.⁵² When the R group is electron releasing (e.g., an alkyl group such as butyl) the acidity of the proton decreases. Likewise, an electron withdrawing R group increases the acidity.⁵² In Table 8.3, the alkyne anion was trapped with D_2O to give the *d*-alkyne (**39**). Strong bases such as MNH₂ (M = Li, K, Na), or *n*-butyllithium in ether (sec. 8.5.G) abstract the proton rapidly at -80° C. Ethylmagnesium bromide is less basic so alkyne deprotonation is slower (30-90 minutes at reflux).⁵² Conjugation enhances the acidity⁵³ (see Table 8.3) and *n*-PrC=C–C=CH reacts instantaneously with ethylmagnesium bromide in refluxing ether. This contrasts with nBuC=CH, which shows no reaction after 15 min under the same reaction conditions, although it reacts slowly when longer reaction times are used.⁵² At higher reaction temperatures, dilithiation [HC=CH \rightarrow HC=C-Li \rightarrow Li-C=C-Li] can be a problem with acetylene. Attempts to form HC=C-M with either *n*-butyllithium (M = Li) or Grignard reagents (M = MgBr) in ether led to M–C=C–M due to the instability of M-C=C-H. In THF, however, both HC=CMgBr and HC=CLi are stable enough below 35°C to be used as nucleophiles in an S_N^2 reaction. Therefore, *n*-butyllithium can be used without problem under the proper conditions (ether, $< -10^{\circ}$ C).

Table 8.3. Effect of Substituents on Alkyne Acidity

R–C≡C–H	$\xrightarrow{\text{NEt}_3, \text{DMF}} P_2O \xrightarrow{\text{R-C=C-D}} 39$
<u>R</u>	Relative Acidity
Ph-	1.0
H-	0.73
n-Bu-	0.058
Cl(CH ₂) ₄ -	0.033
HC=C(CH ₂)	ı- 0.076
MeO-	2.0

The acidity of a terminal alkyne hydrogen leads to another problem when one attempts to form the Grignard reagent of propargyl bromide (40). The initial magnesium insertion reaction generates a Grignard reagent, but migration of the MgBr moiety is possible because of the

^{52. (}a) Reference 32, p 171; (b) Wotiz, J.H.; Hollinsworth, C.A.; Dessy, R.E. J. Org. Chem. 1955, 20, 1545.

^{53.} Reference 32, p 15.

terminal alkyne moiety to form an allene structure (**41**). Allene Grignard **41** is converted to the propynylmagnesium salt (**42**) at temperatures below $0^{\circ}C.^{54}$ Attempts to use the bromomethyl carbon atom in alkyne **40** as a nucleophile should therefore be approached with caution.

$$\begin{array}{c} Br & \xrightarrow{Mg^{\circ}} & BrMg \\ \hline C \equiv C - H & \longrightarrow & H_2C = C = C \\ \hline 40 & & H \end{array} \xrightarrow{MgBr} & H_3C - C \equiv C \vdots & ^+MgBr \\ \hline 41 & & 42 \end{array}$$

When an alkyne possesses a α -proton (like 1-butyne), heating can induce a rearrangement to an internal alkyne (2-butyne) under basic conditions.⁵⁵ In a synthesis of (–)-terpestacin by Jamison and Chan,⁵⁶ for example, heating alkyne **43** with *tert*-butoxide in DMSO gave a 95% yield of **44**. This rearrangement is usually not a problem in S_N2 alkylation reactions involving alkyl halides, at reaction temperatures from ambient to $\approx 120^{\circ}$ C (rearrangement requires much higher temperatures). If the alkylation is sluggish and the reaction requires refluxing in DMF or DMSO however, such rearrangements may be competitive.



8.3.C. Reactions of Alkyne Anions

As noted above, alkyne anions are very useful in $S_N 2$ reactions with alkyl halides and in acyl addition reactions to a carbonyl.⁵⁷ Alkyl halides⁵⁸ and sulfonate esters (tosylates and mesylates primarily) are electrophilic substrates for alkyne anions, as in the conversion of **37** to **38** above. Another example that uses a sulfonate ester leaving group is taken from Sasaki and co-worker's synthesis of the EFGH ring system of ciguatoxin, in which alcohol **45** was first treated triflic anhydride to generate the triflate.⁵⁹ Subsequent reaction with the alkyne anion resulting from the reaction of trimethylsilylacetylene with butyllithium, gave a 61% yield of **46**.

^{54. (}a) Zakharova, A.I. Zh. Obshch. Khim. 1947, 17, 1277; (b) Zakharova, A.I. Ibid. 1949, 19, 1297; (c) Pasternak, Y. Compt. Rend. 1962, 255, 3429; (d) Jacobs, T.L.; Prempree, P. Ibid. 1967, 89, 6177.

 ⁽a) Wotiz, J.H.; Billups, W.E.; Christian, D.T. J. Org. Chem. 1966, 31, 2069; (b) Jacobs, T.L.; Dankner, D. Ibid. 1957, 22, 1424; (c) Bainvel, J.; Wojtkowiak, B.; Romanet, R. Bull. Soc. Chim. Fr. 1963, 978.

^{56.} Chan, J.; Jamison, T.F. J. Am. Chem. Soc. 2003, 125, 11514.

^{57.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 585-605.

^{58.} Porter, N.A.; Chang, V.H.-T.; Magnin, D.R.; Wright, B.T. J. Am. Chem. Soc. 1988, 110, 3554.

^{59.} Sasaki, M.; Noguchi, T.; Tachibana, K. J. Org. Chem. 2002, 67, 3301.



As with cyanide, $S_N 2$ reactions of alkyne anions can be done with substrates other than halides or sulfonate esters. Epoxides are opened by acetylides at the less sterically hindered carbon to give an alkynyl alcohol. A synthetic example is taken from Kishi and co-worker's synthesis of mycolactones A and B, in which reaction of epoxide 47 with the indicated lithium alkyne anion was facilitated by addition of boron trifluoride etherate, to give a 96% yield of 48.⁶⁰



Nucleophilic acyl addition to ketones or aldehydes to give an alkynyl alcohol is the other major synthetic use of alkyne anions. A synthetic example is taken from a synthesis of the C10-C21 segment of lycoperdinoside by Chakraborty and co-workers in which aldehyde **49** reacted with a lithio-alkyne generated form the alkyne and *n*-butyllithium to give a 1:1 mixture of diasteromeric alcohols **50** in >90% yield.⁶¹ The reaction is selective for ketones and aldehydes in the presence of acid derivatives, if the acetylide is not present in large excess.⁶²



A variety of polar substituents can be attached to the C=C unit.⁶³ Alkyne anions show some propensity for 1,2-addition in conjugated systems, especially if the β -carbon of the double bond is hindered.

The reactions of acetylides with carbonyls and halides lead to the following disconnections:

$$R - C \equiv C - R^{1} \bigsqcup^{O} R - X + H - C \equiv C - R^{1} \qquad \begin{array}{c} HO \\ R \xrightarrow{O} \\ R^{1} \end{array} C \equiv C - R^{2} \qquad \begin{array}{c} O \\ R \xrightarrow{O} \\ R \xrightarrow{O} \\ R^{1} \end{array} + H - C \equiv C - R^{2} \end{array}$$

^{60.} Song, F.; Fidanze, S.; Benowitz, A.B.; Kishi, Y. Tetrahedron 2007, 63, 5739.

^{61.} Chakraborty, T.K.; Goswami, R.K.; Sreekanth, M. Tetrahedron Lett. 2007, 48, 4075.

^{62.} Butlin, R.J.; Holmes, R.B.; Mcdonald, E. Tetrahedron Lett. 1988, 29, 2989.

^{63.} Ohkuma, K. Agr. Biol. Chem. (Tokyo) 1965, 29, 962.

Disconnection of the C-//-C=C bond is a high priority when the C=C unit is attached to a primary or secondary carbon, reflecting the facile formation of that bond via the S_N2 reaction. The alkyne moiety is easily converted to a variety of other functional groups, including reduction to alkenes, oxidation to ketones and aldehydes or addition of halides and acid derivatives. Two-carbon or multiple-carbon chain extensions are characteristic of this reaction, and the functional group transforms that are available from alkynes make them highly useful synthons. The ability to reduce alkynes to either the (*E*) or (*Z*) alkene is also of great synthetic value, as discussed in Section 4.9.B for cis reduction, and in Section 4.10.D for trans reduction. Addition reactions (with HX or X_2) were discussed in Sections 2.10.A, 2.10.C. There are several copper-catalyzed coupling reactions of aliphatic and aromatic alkynes, but these are primarily radical mediated reactions and will be discussed in Chapter 13.

8.4 GRIGNARD REAGENTS (C-MG)

8.4.A. Preparation and Properties of Grignard Reagents

Victor Grignard reported what we now call the **Grignard reaction** in 1900,^{64a} and he was awarded the Nobel Prize in 1912. The Grignard reaction is now one of the most important, and powerful in all of organic chemistry, and it set the stage for much of the organometallic chemistry that is so important in modern organic chemistry.^{64b} The so-called **Grignard reagent** (RMgX) is formed by the reaction of magnesium (Mg(0)) with an alkyl or aryl halide, usually in an ether solvent. A simple example is the reaction of bromoethane with magnesium in ether to give **51**.

$$^{\delta+C-Br^{\delta-}}$$
 CH₃CH₂Br + Mg° $\xrightarrow{\text{ether}}$ CH₃CH₂MgBr $^{\delta-C-Mg^{\delta+}-Br}$
51

The importance of the Grignard reagent is seen when the C–Br bond is contrasted with the C–Mg–Br bond. The normal bond polarization in the C–Br bond leads to a positive dipole on carbon, so it is an electrophilic carbon. The C–Mg bond in the Grignard reagent, however, generates a negative dipole on carbon, so it is a nucleophilic carbon. This ability to *invert* the polarity of a carbon atom means the Grignard reagent can function as a carbon nucleophile, usually in reactions with a carbonyl derivative. The reaction was first discovered in 1899 by Barbier, who was Grignard's mentor, although its nature was not well understood at the time.

Barbier discovered that a ketone (such as 52) reacted with magnesium metal, Mg(0), in the presence of iodomethane in ether to give an alcohol (53, after hydrolysis) that resulted



 ⁽a) Grignard, V. Compt. Rend. 1900, 130, 1322; (b) Richey, Jr., H.G. Grignard Reagents. New Developments, John Wiley, Chichester, 2000; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-38; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 284-287.

from coupling of the two organic fragments.⁶⁵ This conversion is now known as the **Barbier reaction** or **Barbier coupling**.^{65,66} Its utility is somewhat limited by the requirement that all reagents be mixed together. In subsequent work, Grignard took the reaction much further. He premixed magnesium metal and the halide, characterized the resulting product as RMgX, and showed how RMgX reacted with many functional groups (particularly with ketones and aldehydes).

Note that there are several modern versions of the Barbier reaction that use transition metals or their derivatives.⁶⁷ Examples include indium metal, samarium iodide, and lead,

although lithium and magnesium can be used. An example, taken from a synthetic approach to the guanacastepenes by Srikrishna and Dethe,⁶⁸ reacted ketone **54** with lithium metal and 4-bromo-1-butene with ultrasound irradiation to give **55**. A retro-Barbier fragmentation has also been reported



in which an alcohol was treated with ten equivalents of bromine and fifteen equivalents of potassium carbonate in chloroform to give a bromo ketone.⁶⁹

When organomagnesium compounds are formed using the Grignard protocol, the reagent is not isolated. In solution, a Grignard reagent (see **56**) is not the simple monomeric species RMgX. Ashby reviewed the composition and discussed the mechanism for formation of Grignard reagents.⁷⁰ Ashby's conclusion was that the reaction proceeds by a single electron transfer (SET) process. Other work involving the formation of aromatic Grignard reagents, however, indicates that no freely diffusing radicals were detectable.⁷¹ The RMgX structure (**56**) usually drawn for a Grignard reagent is in equilibrium with dimethylmagnesium (**57**) and MgBr₂

trimer
$$\implies$$
 dimer \implies 2 RMgX \implies R₂Mg + MgX₂ \implies dimer \implies trimer
56 57

^{65.} Barbier, P. Compt. Rend. 1899, 128, 110.

^{66. (}a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-5; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 58-59.

^{67.} For the use of indium catalyzed reactions in organic synthesis see (a) Chauhan, K.K.; Frost, C.G. J. Chem. Soc. Perkin Trans. 1 2000, 3015. For a list of reagents used in this type of reaction, see (b) Smith, M.B.; March, J. March's Advanced Organic Chemistry, 6th ed.; Wiley, New York, 2007, pp 1302,1313; (c) For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 1126-1133. Also see (d) Blomberg, C. Reactions and Structure. Concepts in Organic Chemistry, Vol. 31. The Barbier Reaction and Related One-Step Processes, Springer Verlag, Berlin, 1993.

^{68.} Srikrishna, A.; Dethe, D.H. Org. Lett. 2004, 6, 165.

^{69.} Zhang, W.-C.; Li, C.-J. J. Org. Chem. 2000, 65, 5831.

^{70.} Ashby, E.C. Quart. Rev. Chem Soc. 1967, 21, 259.

^{71.} Walter, R.I. J. Org. Chem. 2000, 65, 5014.

as well as **58**, in what is called the **Schlenk equilibrium**.⁷² In most common solvents the term Grignard reagent really refers to this equilibrium. It was later reported that dimers such as **59** and **60** were present in ether solutions. The Grignard reagent equilibrium is more complex in ether than it is in THF.⁷³ Smith and Becker verified that the equilibrium favored RMgBr in ether, although there is a mixture.⁷⁴ In THF,⁷⁵ all species (**56-60**) were present and the RMgBr concentration was diminished relative to similar solutions in ether. A Grignard reagent (RMgX) can associate into dimers and trimers in many solvents via a solvent dependent interaction with the halogen.⁷⁶

In other work, Ashby and co-workers concluded⁷⁷ that the Grignard reagent exists primarily as the RMgX species in ether, THF or triethylamine but the composition varies in each solvent. In ether, the monomeric species is largely of RMgX with lesser amounts of R_2Mg and MgX_2 . Association to non-monomeric species is extensive at concentrations > 0.3 M, and the dimers

are assumed to be **59** and **60**. The trimeric structure can be represented as **61**. Ether solutions of Grignard reagents are stable if protected from moisture and air. A 2 N solution of CH_3MgI in ether was stored in a sealed tube for 20 years, and shown to have virtually the same concentration of Grignard reagent as when originally sealed.⁷⁸



In THF, relatively little association occurs and the most abundant monomeric species include both RMgX and $R_2Mg + MgX_2$, as mentioned above. In triethylamine (rarely used as a solvent for Grignard reactions), the only species observed is RMgX for simple alkyl magnesium bromides and chlorides. The amine functions as a Lewis base and coordinates with RMgX, leading to a monomeric species. The solution is more complex for alkyl magnesium iodides or aryl magnesium halides. In hydrocarbon solvents, alkyl halides and Mg(0) react at temperatures >100°C⁷⁹ to give a mixture of insoluble organomagnesium and inorganic magnesium compounds

- 74. Smith, M.B.; Becker, W.E. Tetrahedron Lett. 1965, 3843.
- 75. (a) Smith, M.B.; Becker, W.E. Tetrahedron 1966, 22, 3027; (b) Smith, M.B.; Becker, W.E. Ibid. 1967, 23, 4215.

^{72.} Schlenk, W.; Schlenk, W. Berichte 1929, 62, 920.

^{73. (}a) Whitesides, G.M.; Kaplan, F.; Nagarajan, K.; Roberts, J.D. Proc. Natl. Acad. Sci. 1962, 48, 1112; (b) Ashby, E.C.; Smith, M.B. J. Am. Chem. Soc. 1964, 86, 4363.

^{76. (}a) Walker, F.W.; Ashby, E.C. J. Am. Chem. Soc. **1969**, *91*, 3845; (b) Ashby, E.C.; Walker, F.W. J. Organomet. Chem. **1967**, *7*, P17.

^{77. (}a) Reference 69, p 278; (b) Parris, G.E.; Ashby, E.C. J. Am. Chem. Soc. 1971, 93, 1206.

^{78.} Gilman, H.; Esmay, D.L. J. Org. Chem. 1957, 22, 1011.

^{79.} Ashby, E.C.; Reed, R. J. Org. Chem. 1966, 31, 971.

 $(R_2Mg + MgX_2 + highly associated combinations)$.^{80,79}

Grignard reagents can be formed from primary, secondary and tertiary halides. Alkyl chlorides, bromides or iodides can be used. In all cases, an ether solvent stabilizes the Grignard reagent by forming a Lewis acid-Lewis base charge-transfer complex such as **62**. Coordination with ether also assists in the initial magnesium insertion reaction, and coordination minimizes



decomposition of the Grignard reagent via disproportionation. Aryl and vinyl halides react with magnesium to form aryl magnesium halides such as phenylmagnesium bromide (PhMgBr), or vinyl Grignard reagents such as 1-propenylmagnesium bromide (CH₃CH=CHMgBr). In both cases, the C–Br bond of the aryl or vinyl bromide is stronger than the analogous C–Br bond of an alkyl halide. A stronger Lewis base is required, both to assist the

insertion and to stabilize the organometallic (see **63**). Therefore, a more basic solvent THF is used when aryl or vinyl Grignard reagents must be prepared. Grignard formation occurs in ether, but may be sluggish, and the yields can be poor.

Grignard reagents react as nucleophilic carbanions, and they are also very basic. The conjugate acid of the Grignard is an alkane (MeMgX \rightarrow Me–H), which is a very weak acid (p $K_a = 25-40$).⁸¹ Formation of such a weak conjugate acid suggests that the Grignard reagent is a very strong base. Chevrot et al. showed that methylmagnesium halides are more basic than other straight-chain alkyl or aryl Grignard reagents.⁸¹ Vinyl Grignard reagents and allylic Grignard reagents are slightly more basic than alkylmagnesium halides, and organomagnesium chlorides (RMgCl) are more basic than organomagnesium bromides (RMgBr). This finding may be due to displacement of the Schlenk equilibrium towards RMgX.

The basicity of Grignard reagents is an important factor in their reactions with electrophilic compounds. Grignard reagents react with the slightly acidic hydrogen of water⁸² to give the hydrocarbon (R–H) and a magnesium hydroxide. Alcohols react in a similar manner. Another electrophilic reagent that reacts with Grignard reagents is molecular oxygen, which gives a hydroperoxide anion (**64**) as an initial product. This anion reacts with additional Grignard reagent to give an alkoxide (**65**),⁸² and hydrolysis liberates the alcohol as the final product. The use of anhydrous solvents and exclusion of air is essential for optimum yields in the formation and reactions of Grignard reagents on small scale. On large scale with relatively simple reactants, less care need be taken, because the Grignard reagent will scavenge small amounts of water or other reactive compounds.

 ⁽a) Bryce-Smith, D.; Cox, G.F. J. Chem. Soc. 1961, 1175; (b) Zakharkin, L.I.; Okhlobystin, O. Yu.; Strunin, B.N. Tetrahedron Lett. 1962, 631.

 ⁽a) Chevrot, C.; Folest, J.C.; Troupel, M.; Cachelou, C.; Perichon, J. J. Electroanal. Chem. Interfac. Electrochem. 1974, 55, 263; (b) Chevrot, C.; Folest, J.C.; Troupel, M.; Périchon, J. Ibid. 1974, 54, 135; (c) Chevrot, C.; Folest, J.C.; Troupel, M.; Périchon, J. C.R. Acad. Sci. Ser. C 1971, 273, 613.

^{82.} Reference 67a, pp 794-795 and references cited therein.

$$RMgX + HOH \longrightarrow R-H + HOMgX$$

$$RMgX + O_2 \longrightarrow ROOMgX \xrightarrow{RMgX} 2 ROMgX \longrightarrow 2 ROH$$
64 65

8.4.B. The Reaction with Alkyl and Aryl Halides

By analogy to cyanide or acetylides, a Grignard reagent might be expected to displace an alkyl halide in an S_N2 reaction (RMgX + R¹Y \rightarrow R–R¹). For Grignard reagents derived from simple aliphatic, aryl, or vinyl halides that react with aliphatic alkyl halides, the yield of coupling product (R–R¹) is usually poor. Indeed, if Grignard reagents readily coupled with alkyl halides, Grignard reagents would be difficult to prepare. Only reactive Grignard reagents such as allylmagnesium halides react with alkyl halides that are also highly reactive (iodomethane, allyl bromide, benzyl bromide) to give good yields of a coupling product.⁸³ It is important to note that highly reactive Grignard reagents intended for uses other than coupling are usually prepared in dilute solution with excess magnesium, and via slow addition of the halide to avoid coupling. An example of a successful coupling reaction involves reaction of allyl chloride (**66**) with allylmagnesium chloride to give **67**.⁸⁴ Intramolecular coupling reactions of mesylates at the C3 of indole systems via the *N*-magnesium indole have been reported.⁸⁵



8.4.B.i. The Kharasch Reaction. Alkyl halides are not very reactive in coupling reactions with Grignard reagents. With a few exceptions, good yields of coupling are obtained only by addition of transition metal catalysts.⁸⁶ Kharasch showed the effectiveness of several transition metals that promoted the coupling reaction of phenylmagnesium bromide and chlorodiphenylmethane (**68**, Table 8.4)⁸⁷. It is clear that cobalt chloride (CoCl₂) is very effective and it has been widely used. As shown in Table 8.4, the products of this reaction are the cross coupling product (triphenylmethane, **69**) as well as the symmetrical coupling product (the Wurtz product, **70**, sec. 8.5.B.ii). This transition metal catalyzed coupling reaction is known as the Kharasch reaction. Ferric chloride is a very effective catalyst for the cross coupling of alkyl halides with aryl Grignard reagents, when tetramethylethylenediamine (TMEDA) is

^{83.} Kharasch, M.S.; Reinmuth, O. Grignard Reactions of Nonmetallic Substances, Prentice-Hall, New York, 1954, pp 1054-1056.

^{84.} Chen, L.; Gill, G.B.; Pattenden, G.; Simonian, H. J. Chem. Soc. Perkin Trans. 1 1996, 31.

 ⁽a) Smith III, A.B.; Cui, H. Org. Lett. 2003, 5, 587; (b) Smith III, A.B.; Davulcu, A.H.; Kurti, L. Org. Lett. 2006, 8, 1665.

^{86.} Reference 83, pp 1054-1132.

^{87.} Sayles, D.C.; Kharasch, M.S. J. Org. Chem. 1961, 26, 4210.

used as a stoichiometric additive.⁸⁸ The use of $Fe(acac)_3$ allows coupling with alkyl halides that posses a β -hydrogen.⁸⁹

Thingbi + Fli2CII-C		
68	6	9 70
M	<u>% 69</u>	<u>% 70</u>
No catalyst	0	90
CoCl ₂	82	6
FeCl ₃	63	17
Cu_2Cl_2	30	47
MnCl ₂	0	82

Table 8.4.	Transition	Metal	Catalyzed	Coupling	of	Phenylmagnesium	Bromide	and
	Benzal Bro	mide						

Disproportionation is a serious problem in transition metal catalyzed coupling reactions. Metal-hydrogen exchange followed by Wurtz coupling (sec. 8.5.B.ii) is also a problem. Iron, cobalt, manganese or nickel salts catalyze disproportionation, as shown below for the reaction of cyclopentylmagnesium bromide (71) and ethylmagnesium bromide.⁹⁰ The latter reagent disproportionated to give ethane and ethene, and similar disproportionation of cyclopentylmagnesium bromide gave cyclopentane and cyclopentene. Only a 10% yield of a coupling product (72) was observed, and there no cross-coupling was observed. The reaction of phenylmagnesium and ethylmagnesium bromide behaved similarly, giving an 81% yield of biphenyl.⁹¹



Silver salts are effective catalysts for coupling alkyl Grignard reagents and alkyl halides. The reaction of ethylmagnesium bromide and 1-bromopropane, for example, gave 47% of butane, 12% of hexane, and 37% of the cross-coupled product, pentane.⁹² Disproportionation is less of a problem but the statistical coupling seen in this example is typical, which clearly limits the synthetic utility of the reaction if the cross-coupling product is the desired target. When the target is the symmetrical coupling product (the alkyl groups are the same in the halide and the

^{88.} Nakamura, M.; Matsuo, K.; Ito, S.; Nakamura, E. J. Am. Chem. Soc. 2004, 126, 3686.

^{89.} Nagano, T.; Hayashi, T. Org. Lett. 2004, 6, 1297.

 ⁽a) Kharasch, M.S. Urry, W.H. J. Org. Chem. 1948, 13, 101; (b) Tamura, M.; Kochi, J.K. J. Am. Chem. Soc. 1971, 93, 1485, 1487.

^{91.} Kharasch, M.S.; Fields, J.K. J. Am. Chem. Soc. 1941, 63, 2316.

^{92.} Tamura, M.; Kochi, J.K. J. Am. Chem. Soc. 1971, 93, 1483.

Grignard reagent), however, product yields can be good. Indeed, reaction of ethylmagnesium bromide with bromoethane gave a 92% yield of butane.⁹²

$$RMgBr + Cu^{I}Br \longrightarrow RCu + MgBr_2$$
 $RCu + R^{1}Br \xrightarrow{slow} R-R^1 + Cu^{I}Br$

Cuprous [Cu(I)] salts are readily available, and when mixed with Grignard reagents give excellent yields of cross-coupled products with very little disproportionation.^{92,93} This reaction will be discussed in greater detail in Section 8.7.A. However, a simple example is the reaction of isopropylmagnesium bromide with bromoethane in the presence of cuprous bromide (CuBr), which gaave 2-methylbutane.⁹² The origin of this reaction dates to 1936, and work by Gilman and Straley,⁹⁴ with later work by Cotton and by Kochi,⁹³ and by Noller and co-workers.⁹⁵ Kochi and Tamura studied the mechanism of the reaction,⁹² and proposed an alkylcopper(I) species (RCu) as an intermediate that reacted with the alkyl halide to give the coupled product (R-R') in the rate-determining (slowest) step of the sequence.⁹² The reaction is straightforward with primary alkyl halides,⁹⁶ but secondary and tertiary halides do not react as well. If the concentration of Cu(I) is too high with secondary and tertiary halides, disproportionation occurs. The Grignard reagent, however, can be primary, secondary, tertiary, aryl, or vinyl. A useful example is the conversion of the Grignard reagent of 2-bromo-2-butene (73) to (3Z)-methyl-2-hexene (74) by the Cu(I) catalyzed reaction with iodopropane.⁹⁷ Grignard reagent 73 was enriched in the (Z) isomer, and the reaction proceeded with high stereoselectivity to give predominantly the (Z)-isomer of 74. Organocuprates of this type will be discussed in Section 8.7.A.

$$(Z/E = 90:10)$$
 Me Me MgBr $\xrightarrow{I, THF, Cul}_{-30^{\circ}C}$ Me Me (Z/E = 88:12)

Kochi and Tamura used a different copper catalyst (Li₂CuCl₄, prepared by reaction of LiCl and CuCl₂ in THF) to catalyze the coupling of Grignard reagents and alkyl halides.⁹⁸ An example is taken from a synthesis of bioactive dihydroceramides isolated from the dental pathogen *Porphyromonas gingivalis*, by Smith, Nichols and co-workers,⁹⁹ in which bromide **75** was coupled to Grignard reagent **76** using Li₂CuCl₄ to give a 95% yield of **77**. Note that the coupling occurred with the unprotected hydroxyl group in **75**.

^{93. (}a) Cotton, F.A. Chem. Rev. 1955, 55, 551; (b) Tamura, M.; Kochi, J. J. Organomet. Chem. 1971, 31, 289.

^{94.} Gilman, H.; Straley, J.M. Recl. Trav. Chim. Pays-Bas 1936, 55, 821.

^{95. (}a) Parker, V.D.; Piette, L.H.; Salinger, R.M.; Noller, C.R. J. Am., Chem. Soc. 1964, 86, 1110; (b) Parker, V.D.; Noller, C.R. Ibid. 1964, 86, 1112.

^{96.} Schlosser, M. Angew. Chem. 1974, 86, 751.

^{97.} Derguini-Boumechal, F.; Linstrumelle, G. Tetrahedron Lett. 1976, 3225.

^{98.} Tamura, M.; Kochi, J. Synthesis 1971, 303.

 ⁽a) Mun, J.; Onorato, A.; Nichols, F.C.; Morton, M.D.; Saleh, A.I.; Welzel, M.; Smith, M.B. Org. Biomol. Chem. 2007, 5, 3826; and see (b) Takikawa, H.; Nozawa, D.; Kayo, A.; Muto, S.; Mori, K. J. Chem. Soc., Perkin Trans. 1 1999, 2467.



Coupling of aryl halides and alkylmagnesium halides under these conditions is also possible. Fürstner and Leitner reported that aryl halide couple with Grignard reagents, in the presence of a catalytic amount of an iron catalyst such as $Fe(acac)_2$ to give the arene.¹⁰⁰ An example is the reaction of 2-chloropyridine with hexylmagnesium bromide to give **78** in 90% yield.

$$\overbrace{N}^{C_{6}H_{13}MgBr, 5\% Fe(acac)_{2}, 5 min}_{THF/NMP, 0^{\circ}C \rightarrow rt} \overbrace{N}^{C_{6}H_{13}}_{T6}$$

Metal-catalyzed coupling reactions lead to the disconnection

The coupling reaction of Grignard reagents and cuprous salts does not work well with secondary and tertiary halides, as mentioned above. Similar reagents can be prepared with cuprous salts and organolithium reagents that are much more reactive and give better yields of coupling products. These organocuprate reagents will be discussed in Section 8.7.

8.4.B.ii. Reaction with α -Halocarbonyls. Treatment of a ketone with NBS, NCS, Cl₂, SOCl₂ and so on¹⁰¹ gives an α -chloro ketone, **79**. α -Haloketones give good yields of coupling products with Grignard reagents, even without a transition metal catalyst. There are two electrophilic sites, the carbonyl carbon and the halogen-bearing carbon, but the two are easily differentiated. The halogen-bearing carbon is more susceptible to attack by Grignard reagents. Subsequent reaction with phenylmagnesium bromide gave **80**.¹⁰² This method is superior for

$$\begin{array}{c} O \\ Ph \end{array} \xrightarrow{O} Cl \end{array} \xrightarrow{1. PhMgBr, \\ ether, -30^{\circ}C \rightarrow reflux} O \\ \hline 2. ice/HCl \end{array} \xrightarrow{O} Ph \xrightarrow{O} Ph \\ \hline 80 \end{array}$$

the preparation of α-arylketones, but the yields are often poor if the carbonyl is not conjugated
 to an aromatic nucleus (i.e., with simple alkyl ketone derivatives).

The disconnection for substitution of a α -halo-ketone is



^{100.} Fürstner, A.; Leitner, A. Angew. Chem. Int. Ed. 2002, 41, 609.

102. Ando, T. Yuki Gosei Kagaku Kyokaishi 1959, 17, 777 [Chem. Abstr. 54: 4492b 1960].

 ^{101. (}a) Reed, Jr., S.F. J. Org. Chem. 1965, 30, 2195; (b) Rappe, C.; Kumar, R. Arkiv. Kemi. 1965, 23, 475 [Chem. Abstr. 63: 5521c 1965].; (c) Zbiral, E.; Rasberger, M. Tetrahedron 1969, 25, 1871; (d) Wyman, D.P.; Kaufman, P.R. J. Org. Chem. 1964, 29, 1956.

8.4.C. Reactions with Carbonyl Derivatives

8.4.C.i. Acyl Addition. Grignard reagents react with aldehydes and ketones to give alcohols, in what is commonly called the Grignard reaction.¹⁰³ This reaction is shown for cyclopentanone, which reacts with the nucleophilic isopropylmagnesium bromide at the electrophilic carbonyl carbon to give alkoxide **82**. Hydrolysis is required to liberate the alcohol product, **83**. Ashby suggested the mechanism shown below.¹⁰⁴ It invokes a cyclic transition state (**81**), in which the alkyl group is transferred from magnesium to oxygen, forming the alkoxide and may involve a single electron transfer (SET). This cyclic transition state has stereochemical implications for the alcohol product, since steric and electronic effects will be more important in a cyclic than an acyclic transition state.



The Grignard reaction is one of the best methods to prepare secondary alcohols from aldehydes, since it generates a carbon-carbon bond during the reaction (RMgX + R¹CHO). A simple example is the reaction of 4-methoxyphenylmagnesium bromide and aldehyde **84** to give alcohol **85** in good yield and good diastereoselectivity, in Rozwadowska and Grajewska's synthesis of cytoxazone.¹⁰⁵ With ketones, the reaction generates tertiary alcohols (RMgX + R¹₂C=O \rightarrow RR¹₂CHOH). In McMorris and co-worker's synthesis of (–)-irofulven,¹⁰⁶ **86** reacted with methylmagnesium chloride, to give an 87% yield of **87**. Note the selectivity for addition to the non-conjugated ketone, and delivery of methyl from the top face of **86**, as the molecule is drawn.



^{103.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 1125-1176.

- 105. Grajewska, A.; Rozwadowska, M.D. Tetahedron: Asymmetry 2007, 18, 803.
- 106. McMorris, T.C.; Staake, M.D.; Kelner, M.J. J. Org. Chem. 2004, 69, 619.

^{104.} Reference 70, p 283

MOLECULAR MODELING: Unoccupied Molecular Orbital Maps and Stereoselectivity of Grignard Reactions Involving Diketones

A Grignard reagent is characterized by a δ carbon atom, which reacts as a nucleophile with carbonyl groups. Many Grignard reactions with ketones or aldehydes proceed with good-to-excellent diastereoselectivity. One way to model this is to examine the (unoccupied) molecular orbital on the substrate into which the pair of electrons on the nucleophile ("CH₃", in the case of methylmagnesium chloride) will go, and identify the most electrophilic (electron poor) site for reaction with the nucleophilic (electron rich) carbon of the Grignard reagent. While the LUMO is commonly the "relevant" orbital, in the case of **86** which contains two carbonyl groups, it is not. Here the relevant unoccupied orbital is the next higher-energy orbital ("LUMO+1"). This orbital can be mapped on an electron density surface, and the resulting map employed to see which carbonyl face presents the better target for the nucleophile.

Examine both LUMO (left) and LUMO+1 (right) maps for **86**. On which carbonyl group is the LUMO primarily localized? (By convention, regions where the orbital is most heavily concentrated are colored "blue".) Next, examine the LUMO+1 map. On which carbonyl group is this orbital primarily localized? Which carbonyl face, *syn* or *anti* to the OAc group, is likely to be more susceptible to attack by the nucleophilic Grignard reagent, that is, for which face is the map more blue? Is the product anticipated by the model that which is actually observed?

MOLECULAR MODELING: Transition States and Stereoselectivity of Grignard Reactions of Conjugated Carbonyl Compounds

A more accurate (and more difficult approach) to assigning selectivity Grignard reactions is to compare the energies of the transition states leading from reactants to different isomeric products. For example, addition of methylmagnesium chloride to **86** could conceivably occur onto either the conjugated or non-conjugated carbonyl groups and, for each, *syn* or *anti* to the OAc substituent. The major product (**87**) follows from addition to the non-conjugated carbonyl *anti* to OAc. Application of transition state models, which requires that the transition state for each of these four possibilities be found, and the lowest-energy transition state be identified, is beyond the scope of *SpartanModel*. We will limit ourselves to examining results obtained using *Spartan*.

Transition states for addition of methyl magnesium chloride *syn* and *anti* to the non-conjugated carbonyl (top left and right), and *syn* and *anti* to the conjugated carbonyl (bottom left and right) appear on screen. Relative energies are as follows: *anti* to non-conjugated carbonyl, 0 kJ/mol; *syn* to conjugated carbonyl, 8; *syn* to non-conjugated carbonyl, 33; *anti* to conjugated carbonyl, 99. The lowest-energy transition state is for addition *anti* to non-conjugated carbonyl group and leads to the observed major product. The model shows a switch in the preferred stereochemistry of reaction between addition to the non-conjugated carbonyl groups. *Anti* addition is favored for the non-conjugated carbonyl group *syn* addition is favored for the conjugated carbonyl group is only 8 kJ/mol. Which transition state for addition to the non-conjugated carbonyl group over (*syn*) addition to the lengths of the CC bond that is being formed and the CO double bond that is being converted to a single bond.) Is this the result you expect? Elaborate.

The disconnection for this process is

8.4.C.ii. Acyl Substitution. Although the reaction with aldehydes and ketones is the most common, Grignard reagents react with most other carbonyl derivatives.¹⁰⁷ As we saw in Section 2.5.C, acid derivatives contain a leaving group such as Cl, O_2R , OR, or NR₂, and react with nucleophiles via acyl substitution. Initial addition of a Grignard reagent to the acyl carbon of an acid derivative generates an alkoxide intermediate (**88**), called a **tetrahedral intermediate**, and displacement of the leaving group (X) leads to a ketone. If the initially formed ketone product is more reactive than the acid derivative starting material, further reaction with the Grignard reagent can give tertiary alcohol **90** via alkoxide **89**.¹⁰⁸ The competition between the ketone product and the acyl starting material can lead to mixtures of products, and there may be significant amounts of unreacted starting material.

$$\begin{array}{c} O \\ R \xrightarrow{R^{1}MgX} \\ R \xrightarrow{R^{1}} X \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \end{array} \xrightarrow{R} \begin{array}{c} O \\ R \xrightarrow{R^{1}MgX} \\ R^{1} \\ \end{array} \xrightarrow{R^{1}MgX} \left[\begin{array}{c} O \\ R \xrightarrow{R^{1}MgX} \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \right] \xrightarrow{R} \begin{array}{c} O \\ R \xrightarrow{R^{1}MgX} \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} R^{1} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ R \xrightarrow{R^{1}} \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array} \xrightarrow{R^{1}} \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array} \xrightarrow{R^{1}} \begin{array}{R^{1}} \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array} \xrightarrow{R^{1}} \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array} \xrightarrow{R^{1}} \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array} \xrightarrow{R^{1}} \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array} \xrightarrow{R^{1}} \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array} \xrightarrow{R^{1}} \begin{array}{c} O \\ \end{array}$$

Acid chlorides are the most reactive acid derivatives, where chlorine is the leaving group.¹⁰⁹ Reaction of Grignard reagents with acid chlorides gives excellent yields of the tertiary alcohol when an excess of the Grignard reagent is used, especially under vigorous reaction conditions. When the reaction is done at low temperatures and/or when metal catalysts are added, isolation of the ketone product is often possible.¹¹⁰ In some cases, the ketone product can be isolated. Reaction of hexanoyl chloride and **91**, taken from Dussalt and co-worker's synthesis of peroxyacarnoate A,¹¹¹ gave a 78% yield of ketone **92**.



An excellent method for converting an acid chloride to a ketone employs transition metal catalysts such as ferric chloride, in conjunction with low reaction temperatures.¹¹² Reaction

- 111. Xu, C.; Raible, J.M.; Dussault, P.H. Org. Lett. 2005, 7, 2509.
- 112. Cason, J.; Kraus, K.W. J. Org. Chem. 1961, 26, 1768, 1772.

^{107.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, **1999**, pp 1389-1411.

^{108. (}a) Reference 82, pp 567-568; (b) Reference 83

^{109.} For a review of reactions of acyl chlorides with organometallic reagents, see Dieter, R.K. *Tetrahedron* 1999, 55, 4177.

^{110.} Stowell, J.C. J. Org. Chem. 1976, 41, 560.

of butylmagnesium bromide with octanoyl chloride at -60°C gave a mixture of 13% of **93**, 4% of **94** (from the secondary reaction of butyl-magnesium bromide and **93**, and 60% of **95**.¹¹² When a catalytic amount (2 mol %) of ferric chloride (FeCl₃) was added, however, a 76% yield of ketone **93** was obtained along with 3% of the over alkylation product, **94**.¹¹² If the intermediate ketone is unreactive to nucleophilic substitution due steric hindrance or peculiar electronic factors (diisopropyl ketone and phenyl-*tert*-butyl ketone are both sterically hindered), the ketone can usually be isolated (sec. 8.4.G for problems with hindered ketones). In many instances, however, even dry ice temperatures and reverse addition techniques give poor yields of the ketone.¹¹³

$$n-C_{6}H_{13} \xrightarrow{O}_{C1} \underbrace{1. n-C_{4}H_{9}MgBr, cat}_{2. H_{3}O^{+}} \xrightarrow{O}_{n-C_{6}H_{13}} \xrightarrow{O}_{n-C_{4}H_{9}} + \underbrace{OH}_{n-C_{6}H_{13}} \xrightarrow{OH}_{n-C_{4}H_{9}} + \underbrace{OH}_{n-C_{6}H_{13}} \xrightarrow{O}_{n-C_{4}H_{9}} + \underbrace{OH}_{n-C_{6}H_{13}} \xrightarrow{O}_{n-C_{6}H_{13}} \xrightarrow{O}_{OH}$$

$$\underbrace{93}_{catalyst = NONE, -60^{\circ}C}_{catalyst = 2\% FeCl_{3}, -60^{\circ}C} \xrightarrow{13\%}_{76\%} \xrightarrow{4\%}_{3\%} \xrightarrow{4\%}_{3\%} \xrightarrow{60\%}_{15\%}$$

Changing the metal from magnesium to one that gives a less reactive organometallic provides an alternative method for isolating the ketone. Gilman and co-workers¹¹⁴ discovered that a Grignard reagent reacts with cadmium chloride (CdCl₂) to give a dialkylcadmium reagent (R₂Cd), and this less reactive organometallic is more selective in its reactions with carbonyl derivatives.¹¹⁵ This reaction is rather slow, however, and in many cases it is not clear that dialkylcadmium is the active reagent.¹¹⁶ Dialkylcadmium reagents are readily formed from primary Grignard reagents, but secondary and tertiary organocadmium reagents are relatively unstable.¹¹⁷ The likely decomposition pathway is dissociation to radicals, which disproportionate to give alkane and alkene products. Reagents such as di-*n*-pentylcadmium (**96**) are formed by reaction of a Grignard reagent (pentylmagnesium bromide) and anhydrous cadmium chloride (CdCl₂). Such reagents react rapidly with acyl halides but very slowly or not at all with ketones, aldehydes, esters or amides. The yields of ketone products obtained by reaction with acid chlorides are moderate to good.¹¹⁸ In general, dialkylcadmium reagents do not react with the ketone products, but there are exceptions when highly reactive ketone products are formed.¹¹⁵ When **96** reacted with α -chloroacetyl chloride, a 46% yield of **97** was obtained.¹¹⁸

^{113.} Newman, M.S.; Smith, A.S. J. Org. Chem. 1948, 13, 592.

^{114. (}a) Gilman, H.; Nelson, J.F. *Rec. Trav. Chim.* 1936, 55, 518; (b) Cason, J. J. Org. Chem. 1948, 13, 227; (c) Le Guilly, L.; Tatibouët, F. Compt. Rend. Ser. C 1966, 262, 217; (d) LeGuilly, L.; Chenault, J.; Tatibouët, F. Ibid. 1965, 260, 6634.

^{115. (}a) Cason, J. Chem. Rev. 1947, 40, 15; (b) Shirley, D.A. Org. React. 1954, 8, 28 (see pp 35-38).

^{116.} Cason, J. J. Am. Chem. Soc. 1946, 68, 2078.

^{117.} Cason, J.; Fessenden, R.J. J. Org. Chem. 1960, 25, 477.

⁽a) Miyano, M.; Dorn, C.R.; Mueller, R.A. J. Org. Chem. 1972, 37, 1810; (b) Miyano, M.; Dorn, C.R. *Tetrahedron Lett.* 1969, 1615; (c) Archer, S.; Unser, M.J.; Froelich, E. J. Am. Chem. Soc. 1956, 78, 6182; (d) Bindra, J.S.; Bindra, R. Prostaglandin Synthesis, Academic Press, New York, 1973, pp 52-53.



Although esters are much less reactive than acid chlorides (ethoxy is a poorer leaving group than Cl), they are only slightly less reactive than the ketone products resulting from reaction with a Grignard reagent. A Grignard reaction with esters rarely gives the ketone in good yield. A mixture of ester, ketone and tertiary alcohol is often observed when only one equivalent each of Grignard reagent and ester are used. Two or more equivalents of Grignard reagent give the alcohol as the only product.¹¹⁹ The tendency for over-reaction of some acid derivatives can have useful synthetic applications. The reaction of **98** with an excess of methylmagnesium bromide¹²⁰ illustrates the reaction at hand, but introduces an interesting feature. If we focus on

the benzyl ester, addition of two equivalents of Grignard reagent leads to the tertiary alcohol in **99**. The acetate group in **98** is also an ester, and reaction with MeMgBr leads to the alcohol unit in **99** and *tert*-butanol (via loss of acetone



from initial addition of MeMgBr and subsequent reaction of acetone to give the alcohol). We have previously seen another application of this reaction in the **Barbier-Wieland degradation** (sec. 3.7.A.iv.),¹²¹ used to decrease the chain length of carboxylic acid esters by one carbon.

The usual disconnections for reaction with esters and acid chlorides are

$$\underset{R \xrightarrow{II}}{\overset{O}{\amalg}} R^{1} \xrightarrow{C} R - COX + 2 R^{1} - X \qquad R \xrightarrow{OH}{\overset{O}{\amalg}} R^{1} \xrightarrow{C} R - CO_{2}H + 2 R^{1} - X$$

Alkyl esters such as *n*-butyl mesitoate (100) resist the acyl addition reaction because the ortho methyl groups sterically hinder the acyl carbon. When 100 reacted with phenylmagnesium iodide, for example, the products were mesitoic acid (101) and iodobutane.¹²² Acyl addition is inhibited by the presence of the methyl groups, but iodide (assisted by Mg²⁺ complexation with the carbonyl) attacks the O–C group (O–Bu in 100) via an S_N2 reaction that displaces the



^{119.} Fieser, L.F.; Heymann, H. J. Am. Chem. Soc. 1942, 64, 376.

- 121. (a) Wieland, H. Berichte 1912, 45, 484; (b) Barbier, P.; Locquin, R. Compt. Rend. 1913, 156, 1443.
- 122. (a) Reference 83, p 567; (b) Fuson, R.C.; Bottorff, E.M.; Speck, S.B. J. Am. Chem. Soc. 1942, 64, 1450.

^{120.} Evans, D.A.; Barnes, D.M.; Johnson, J.S.; Lectka, T.; von Matt, P.; Miller, S.J.; Murry, J.A.; Norcross, R.D.; Shaughnessy, E.A.; Campos, K.R. J. Am. Chem. Soc. 1999, 121, 7582.

carboxyl moiety (which functions as a leaving group). Grignard reactions with lactones are interesting in that ring opening accompanies acyl addition, giving a diol in which the two ends are differentiated. Valerolactone, for example, reacted with butylmagnesium iodide to give 5-methyl-1,5-hexanediol. Amides are less reactive than esters (NR₂ is a poorer leaving group than OR) and the ketone product can often be isolated, although the yields are usually poor. Reaction of *N*-methylacetamide with two equivalents of phenylmagnesium bromide gave alkoxide **102**.¹²³ Hydrolysis led to loss of the amine (via **103**) and formation of the ketone product. Since **102** cannot react with additional Grignard, the product is the ketone. *N*,*N*-Dialkyl amides also react with Grignard reagents to give a ketone, but as mentioned above, the yields are usually poor.¹²⁴ An exception is a Weinreb amide, which we have seen previously (see sec. 2.5.C). This activated amide –CONMe(OMe) is an excellent leaving group, and the reaction stops at the ketone. In a synthesis of naamidine A by Watson and co-workers, amide **104** was converted to ketone **105** in 62% yield, by reaction with the Grignard reagent shown.¹²⁵



The reaction with lactams follows a somewhat different pathway than that just described for amides. The final product is an amine or an amino ketone. 2-Pyrrolidinone and 2-piperidone derivatives give primarily the amine, with minor amounts of ring cleavage products (amino ketones). At low temperature, however, the ring-opened ketone can be obtained, as in Martin and Simila's synthesis of the azatricyclic skeleton of FR901483 in which *N*-Boc-2-pyrrolidinone (**106**) reacted with the butenylmagnesium bromide to give iminium salt **107** which opened to give **108** in 98% yield after hydrolysis.^{126a} Larger ring lactams give mainly the amino ketone, as in the reaction of *N*-methyl caprolactam with ethylmagnesium bromide to give a mixture of dialkylamine **109** in 42% yield and the ring-opened amino ketone in 23% yield .^{126b}

^{123.} Heyns, K.; Pyrus, W. Chem. Ber. 1955, 88, 678.

^{124.} Busch, M.; Fleischmann, M. Berichte 1910, 43, 2553.

^{125.} Aberle, N.S.; Lessene, G.; Watson, K.G. Org. Lett. 2006, 8, 419.

^{126. (}a) Simila, S.T.M.; Martin, S.F. J. Org. Chem. 2007, 72, 5342; (b) Lukes, R.; Dudek, V.; Sedláková, O.; Korán, J. Coll. Czech. Chem. Commun. 1961, 26, 1105.



8.4.C.iii. Reaction with Nitriles. Nitriles are carboxylic acid derivatives and react with Grignard reagents (also sec. 8.2.C).¹²⁷ Initial attack generates an intermediate iminium salt that can be hydrolyzed (with loss of ammonia) to the corresponding ketone.¹²⁸ The best yields are obtained with aryl nitriles, as illustrated by the reaction of 3-methoxybenzonitrile with the Grignard reagent derived from 4-bromo-1-butene. The initial reaction generates iminium salt 110,¹²⁹ and subsequent hydrolysis produced ketone 111. When an alkyl nitrile reacts with a Grignard derived from an hindered alkyl halide, the yield of ketone can be poor, but this is not always the case. Reaction of cyclopropanecarbonitrile (112) and isopropylmagnesium bromide gave > 80% of ketone 113 (R = i-Pr).¹³⁰ The intermediate iminium salt is not usually isolated since hydrolysis to the ketone is rapid. Hindered iminium salts can resist hydrolysis due to steric blocking of the imino carbon, however, and treatment with aqueous acid¹³¹ under vigorous conditions can be required to give even modest yields. Reaction of 112 with tertbutylmagnesium bromide, followed by heating at reflux with 1 N HCl, gave only 35% of **113** (R = t-Bu).^{130a} Hindered nitriles often give no reaction at all when they are reacted with very hindered Grignard reagents. Reaction of tert-butylmagnesium chloride with cyanomethyl-2,4,6-trimethylbenzene, for example, gave 0% of the ketone.¹³²



132. Bruylants, A. Bull. Soc. Chem. Fr. 1958, 1291.

^{127.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 1420-1422.

^{128.} Reference 83, pp 767-845.

^{129.} Taber, D.F.; Wang, Y.; Pahutski, Jr., T.F. J. Org. Chem. 2000, 65, 3861.

 ^{130. (}a) Hrubiec, R.T.; Smith, M.B. J. Org. Chem. 1984, 49, 431; (b) Hanack, M.; Ensslin, H.M. Annalen 1966, 697, 100; (c) Hanack, M.; Bocher, S.; Herterich, I.; Hummel, K.; Vött, V. J.L. Ann. Chem. 1970, 733, 5.

^{131.} Citron J.D.; Becker, E.I. Can. J. Chem. 1963, 41, 1260.

The disconnection for the nitrile-Grignard reagent reaction is:

$$\bigcap_{R \to R^{1}}^{O} R^{-} C = N^{+} R^{1} - X$$

8.4.C.iv. Reaction with Carbon Dioxide. Carbon dioxide (CO₂, O=C=O) is actually a carbonyl derivative, and reacts with a Grignard reagent¹³³ to give a carboxylate salt, that gives the corresponding carboxylic acid upon hydrolysis.¹³⁴ Conversion of benzylmagnesium bromide to phenylacetic acid¹³⁵ is an example of this transformation. This functional group interchange of a halide to an acid proceeds with a one-carbon extension of the chain. An interesting example is taken from a synthesis of (+)-biotin by Seki and co-workers,¹³⁶ in which nitrile **114** was generated *in situ*, and reacted with the bis(Grignard) reagent shown. Initial reaction with the nitrile led to formation of the ketone unit in **115** after hydrolysis (see sec 8.4.C.iii above), but the second C–MgBr unit reacted with carbon dioxide and hydrolysis with aqueous citric acid generated the carboxylic unit. The yield of **115** was 79% in the solvent shown, but the yield was significantly less in THF and other solvents.



The disconnection for the carboxylation reaction is

$$R - CO_2H \longrightarrow R - X + CO_2$$

8.4.D. Conjugate Addition

 α , β -Unsaturated carbonyl derivatives have two reactive sites, and nucleophilic addition of a Grignard reagent can occur at either the acyl carbon (1,2-addition) or the alkenyl carbon (1,4-addition). When a Grignard reagent reacts with a conjugated carbonyl such as **116**, the 1,4-addition product is an enolate anion (**117**, see sec. 9.2). The 1,2-addition product is the usual alkoxide **118**. The course of this reaction varies with the steric bulk of R¹ in the Grignard reagent, and R in the carbonyl compound. As the size of R increases, the amount of 1,4-addition

 ⁽a) Oppolzer, W.; Kündig, E.P.; Bishop, P.M.; Perret, C. *Tetrahedron Lett.* 1982, 23, 3901; (b) Rowsell, D.G. Brit. Patent 1,392,907 [*Chem. Abstr.* 83: P114682t 1975].

 ⁽a) Sneeden, R.P.A. in *The Chemistry of Carboxylic Acids and Esters*, Patai, S. (Ed.), Interscience, New York, *1969*, pp. 137-175; (b) Reference 83, pp 913-948.

^{135.} Eberson, L. Acta Chem. Scand. 1962, 16, 781.

^{136.} Seki, M.; Mori, Y.; Hatsuda, M. Yamada, S. J. Org. Chem. 2002, 67, 5527.

increases, although α , β -unsaturated aldehydes usually give only 1,2-addition.¹³⁷ Conversely, as the R¹ group of the Grignard increases in size, less conjugate addition is observed for a given R. In general, Grignard reagents undergo 1,2-addition with conjugated aldehydes and relatively unhindered conjugated ketones, although conjugate alkylation often competes in the latter case. In a synthesis of (+)-methynolide,¹³⁸ Cossy and co-worker's reacted methacrolein with ethylmagnesium bromide, and obtained a 68% yield of the 1,2-addition product, **119**.



In Table 8.5¹³⁹ the influence of R² (from the Grignard reagent) and R¹ (attached to the carbonyl) on the percentage of conjugate addition is shown for reaction of alkyl Grignard reagents with **120**. Note that the phenyl group in **120** (R³ = Ph, R⁴ = H) has a significant influence on the reaction (see below), which proceeds by a six-center transition state (see **121**) to give the conjugate addition product, **122**. As R¹ in **120** becomes larger, attack at the carbonyl (path *a*) in a four-center transition state induces a large and destabilizing R²⇔R¹ interaction leading to preferred attack at the end of the planar conjugated system (path *b*). When R¹ is small, R² is easily transferred to the carbonyl by the usual four-center transition state (path *a*).¹⁴¹ Increasing the size of R³ or R⁴ increases the magnitude of the R³(R⁴)⇔R² interaction in the six-center transition state (path *b*), diminishing the amount of 1,4-addition. Removing the Lewis acid byproduct (MgX₂) facilitates formation of **121** with an increase in 1,4 addition product **122**.¹⁴⁰ With alkylidene malonates and related compounds, virtually no 1,2-addition is observed,¹⁴⁰ although two electron-withdrawing groups attached to the alkene moiety make conjugate addition rather facile.

^{137.} Hauser, F.M.; Hewawasam, P.; Rho, Y.S. J. Org. Chem. 1989, 54, 5110.

^{138.} Cossy, J.; Bauer, D.; Bellosta, V. Tetrahedron 2002, 58, 5909.

^{139.} Maroni-Barnaud, Y.; Maroni, P.; Fualdès, A.M. Compt. Rend. 1962, 254, 2360.

^{140.} Mane, R.B.; Krishna Rao, G.S. J. Chem. Soc. Perkin Trans. 1 1973, 1806.

$R^{2} - MgCl + \frac{R^{3} O}{R^{4}} R^{1} \rightarrow 120$	$\mathbf{R}^{2} - \mathbf{Mg} \cdot \mathbf{WX}$ $\mathbf{R}^{3} - \mathbf{Mg} \cdot \mathbf{WX}$ $\mathbf{R}^{3} - \mathbf{R}^{4} - \mathbf{W}$ $\mathbf{R}^{4} - \mathbf{W}$ $121 - \mathbf{U}$	$\rightarrow H_{3}O^{+}$	$R^{3} \xrightarrow{R^{2}} O$ $R^{4} \xrightarrow{R^{1}} R^{1}$ 122
<u>R</u> ¹	<u>R</u>	<u>% 122</u>	
Ме	<i>i</i> -Pr	50	
Me	t-Bu	33	
<i>t</i> -Bu	<i>i</i> -Pr	60	
<i>t</i> -Bu	<i>t</i> -Bu	48	
Ph	<i>i</i> -Pr	66	
Ph	<i>t</i> -Bu	67	
PhCH=CH-	<i>i</i> -Pr	70	
PhCH=CH-	<i>t</i> -Bu	93	

Table 8.5. Effect of Steric Hindrance on 1,4- vs. 1,2-Addition to α , β -Unsaturated Ketones

A similar transition state can be drawn for the reaction of Grignard reagents and α , β unsaturated esters, where steric hindrance in the ester moiety partially blocks the acyl carbon and leads to more 1,4-addition.¹⁴¹ An example is the reaction of butylmagnesium bromide with *sec*-butylcrotonate to give *sec*-butyloctanoate.¹⁴² Asymmetric induction is possible in these reactions, as illustrated by the reaction of the (–)-menthyl ester¹⁴³ of crotonic acid **123** to give the (*S*)-(+) enantiomer of 3-phenyl derivative **124** in 46% yield.¹⁴⁴ Interestingly, addition of Cu₂Cl₂ to the reaction gave the (*R*)-(–) enantiomer.



In general, addition of cuprous [Cu(I)] salts to a Grignard facilitates conjugate addition, partly because a more highly reactive species (R₂MgCu or RCu) is formed, and partly because copper coordinates better to the carbonyl, which facilitates the six-center transition state. The organocuprates derived from organolithium reagents (R₂CuLi, sec. 8.7.A) are extremely useful in conjugate addition reactions.¹⁴⁵ Organocopper reagents derived from the reaction of a Grignard reagent with a cuprous salt, however, are also very useful. In a synthesis of *N*-deacetyllappaconitine by Taber and co-workers, butenylmagnesium bromide reacted with

^{141.} Munch-Petersen, J. J. Org. Chem. 1957, 22, 170.

^{142.} Munch-Petersen, J.; Jacobsen, S. Compt. Rend. 1962, 255, 1355.

^{143.} Seiji, S.; Yumiko, S.; Sawada, S.; Sejima, Y.; Ohi, S.; Shunsuke, O.; Inouye, Y. *Bull Kyoto Univ. Educ. Ser. B*, *1979*, *55*, 33 [*Chem. Abstr.* 92: 129098s *1980*].

^{144.} Inouye, Y.; Walborsky, H.M. J. Org. Chem. 1962, 27, 2706.

^{145. (}a) Bernady, K.F.; Weiss, M.J. Prostaglandins 1973, 3, 505; (b) Reference 118d, p 111.

conjugated ketone **125** in the presence of CuBr–SMe₂ and triethylsilyl chloride to give a 78% yield of the conjugate addition product **126**.¹⁴⁶ This example is typical in that cuprous salts generally lead to 1,4-addition, despite the usual propensity of conjugated aldehyde to give 1,2-addition with nucleophiles. A variety of conjugated carbonyl derivatives undergo 1,4-addition with Grignard reagents. Conjugate addition to α , β -unsaturated amides is known and proceeds with little variation from the results observed for conjugated ketones or esters.¹⁴⁷ As mentioned above, the organocuprates derived from lithium will be discussed in greater detail in Section 8.7.A.



8.4.E. Reaction with Epoxides¹⁴⁸

Grignard reagents react with epoxides to form a new carbon-carbon bond with opening of the three-membered ring to give an alcohol after hydrolysis. There are two electrophilic carbon atoms, and the Grignard reagent attacks the less hindered carbon in an $S_N 2$ like reaction.¹⁴⁹ If the carbons of the epoxide moiety are primary or secondary, attack can occur at either carbon leading to a mixture of alcohol products. When 2-ethyloxirane reacts with methylmagnesium bromide, attack at the primary carbon gave 3-pentanol with only trace amounts of attack at the secondary carbon. When the epoxide has substituents that provide equal or close to equal steric hindrance at each carbon, as in 2-ethyl-3-propyloxirane the reaction produces a mixture of regioisomeric alcohol products. In this case, reaction of this epoxide and methylmagnesium bromide gave a mixture of 4-methyl-3-heptanol and 3-methyl-4-heptanol. When a Grignard reagent opens an epoxide, the new substituent is on the β -carbon relative to the OH.



Metal salts such as cuprous ion promotes the ring opening reaction of epoxides, which is particularly useful for directing the incoming Grignard reagent to a particular carbon (to make

^{146.} Taber, D.F.; Liang, J.-L.; Chen, B.; Cai, L. J. Org. Chem. 2005, 70, 8739.

^{147.} Gilbert, G.; Aycock, B.F. J. Org. Chem. 1957, 22, 1013.

⁽a) Taylor, S.K.; Haberkamp, W.C.; Brooks, D.W.; Whittern, D.N. J. Heterocyclic Chem. 1983, 20, 1745;
(b) Linstrumelle, G.; Lorne, R.; Dang, H.P. Tetrahedron Lett. 1978, 4069;
(c) Boireau, G.; Namy, J.L.; Abenhaïm, D. Bull. Soc. Chim. Fr. 1972, 1042.

^{149.} Sano, M.; Kodama, H.; Matsuda, H.; Matsuda, S. Nippon Kagaku Kaishi 1974, 1716 [Chem. Abstr. 82: 42560f 1975].

the reaction more regioselective). An example is taken from Martín and co-worker's synthesis of (+)-muconin in which the reaction of epoxide **127** with 1-undecylmagensium bromide (formed *in situ*) and cuprous iodide,¹⁵⁰ gave **128** in 70% yield. Note that the Grignard reagent added to the less substituted carbon. Allylic epoxides can be opened in a conjugated addition manner using Grignard reagents, analogous to an S_N2' reaction (sec. 2.6.A.iii). Isopropylmagnesium bromide reacted with **129**, for example, attacking the alkene unit with concomitant opening of the epoxide to give a 76% yield of **130** with a 22.1:1.0 Z:E ratio.¹⁵¹



This fundamental reaction leads to useful synthetic applications. Similar alkylation of aryl epoxides, followed by oxidation of the resulting alcohol, makes the Grignard-epoxide reaction an effective route for the synthesis of α -aryl ketones. Epoxidation of cyclohexene with *m*-chloroperoxybenzoic acid (sec. 3.4.B.iii) gave cyclohexene oxide. Reaction with phenylmagnesium bromide and hydrolysis led to 2-phenylcyclohexanol. Oxidation of the secondary alcohol moiety with chromium trioxide (or with another oxidizing agent as in sec. 3.2) gave the targeted 2-phenylcyclohexanone.

This sequence generates the useful disconnections:

$$\begin{bmatrix} R \\ R \\ R \end{bmatrix}^{OH} \xrightarrow{R}_{R} \xrightarrow{R} \xrightarrow{R}_{R} \xrightarrow{R}_{R} \xrightarrow{R}_{R} \xrightarrow{R}_{R} \xrightarrow{R}$$

Looking back to the Schlenk equilibrium (sec 8.4.A), Grignard reagents contain the mild Lewis acid MgX₂ even if no other reagent is added. This Lewis acid is part of the reagent, and it can induce acid catalyzed rearrangements of acid-sensitive epoxides, complicating the normal product distribution. When 5,6 β -epoxycholestane (**131**) was treated with methylmagnesium iodide, the product was 4a α -methyl-A-homo- β -norcholestan-4a β -ol, **134**,¹⁵² which is explained by reaction of the epoxide with MgI₂ to give **132**. A 1,2-hydride shift (secs. 2.6.B.iii, sec. 12.2.B) generated ketone derivative **133**, which reacted with additional methylmagnesium

^{150.} Pinacho Crisostomo, F.R.; Carrillo, R.; Leon, L.G.; Martin, T.; Padron J.M.; Martin, V.S. J. Org. Chem. 2006, 71, 2339

^{151.} Taber, D.F.; Mitten, J.V. J. Org. Chem. 2002, 67, 3847.

^{152.} Frankel, J.J.; Julia, S.; Richard-Neuville, C. Bull. Soc. Chim. Fr. 1968, 4870.

iodide to give the alcohol (134). The involvement of MgI_2 in the conversion of 131 to 134 was later substantiated by similar reaction of a cholestan-3-one derivative with methylmagnesium iodide.¹⁵³ The yield was low, since cationic rearrangement was slower than nucleophilic attack in the aprotic solvent used for this Grignard reaction.



If the epoxide moiety is attached to a tertiary carbon, cationic rearrangements can lead to significant amounts of rearranged product. The cationic intermediate generated from the epoxide and MgX_2 does not always rearrange to a ketone derivative, but can give $S_N 1$ type reactions if a tertiary center is present. Reaction of phenylmagnesium bromide with epoxide **135**, for example, led to a coordination complex of the magnesium and oxygen in **136**. The oxonium salt opened to generate an oxygen-stabilized cation (**137**), which is particularly stable. When this intermediate reacted with the nucleophilic PhMgBr reagent, the product was alcohol **138** after hydrolysis.¹⁵⁴ It should be noted that in epoxy-ketones or epoxy-aldehydes, opening the epoxide ring is usually slower than addition to the carbonyl.¹⁵⁵



 ^{153. (}a) Rao, P.N.; Uroda, J.C. *Tetrahedron Lett.* 1964, 1117; (b) Hall, N.D.; Just, G. *Steroids* 1965, 6, 111; (c) Julia, S.; Lavaux, J.P.; Lorne, R.; Riz, J.-C. *Bull. Soc. Chim. Fr.* 1967, 3218.

^{154.} Stevens, C.L.; Holland, W. J. Org. Chem. 1958, 23, 781.

^{155.} Sepúlveda, J.; Soto, S.; Mestres, R. Bull. Soc. Chim. Fr., Part 2 1983, 233.
8.4.F. Selectivity in Grignard Reactions

8.4.F.i. Configurational Stability of Grignard Reagents. In principle, the carbon atom bearing a MgX unit can be a stereogenic center, which has important stereochemical implications for any reaction. When the C–Mg bond of a Grignard reagent is formed, however, the stereochemical integrity of that bond is poor. For this reason, the generation and use of chiral Grignard reagents is *not* a synthetically useful option in most systems. The NMR studies by Roberts and Whitesides ¹⁵⁶ and also Fraenkel and co-workers¹⁵⁷ on Grignard regents in ether, established that the C–Mg has significant ionic character and undergoes rapid inversion at the magnesium-bearing carbon atom. 3-Cyclohexenylmagnesium bromide (**139**),

MgBr
 for example, undergoes inversion of configuration at the C–Mg position. The rate of inversion decreased when the solvent was changed from ether to THF.¹⁵⁸
 Fraenkel and co-workers also showed that 2-butylmagnesium bromide (140)

undergoes rapid inversion at ordinary temperatures,^{157,159} thereby making a Grignard reagent derived from chiral 2-butyl bromide effectively racemic. However, Hoffmann and Hölzer used chiral Grignard reagent **141**, which was



configurationally stable at -78° C.¹⁶⁰ In a nickel-catalyzed reaction of **141** with vinyl bromide, the so-called **Kumada-Corriu coupling**,¹⁶¹ an 80% yield of **142** was obtained in 89% ee, along with 11% of 1-phenyl-1-butene. Grignard reagent **141** was generated by the reaction of a chiral chlorosulfone with an excess of ethylmagnesium chloride at -78° C.



Since the carbon-magnesium bond is stereochemically unstable, a Grignard reagent derived from a chiral halide equilibrate $(143a \rightarrow 143b)$,¹⁶² so subsequent Grignard reaction with an aldehyde or ketone will give racemic products. There are a few exceptions to this configurational instability. Walborsky et al. reported that the Grignard reagent derived from 144 reacted with

^{156.} Whitesides, G.M.; Roberts, J.D. J. Am. Chem. Soc. 1965, 87, 4878.

^{157. (}a) Fraenkel, G.; Dix, D.T. J. Am. Chem. Soc. 1966, 88, 979; (b) Fraenkel, G.; Dix, D.T.; Adams, D.G. Tetrahedron Lett. 1964, 3155.

^{158.} Maercker, A.; Geuss, R. Angew. Chem. Int. Ed. 1971, 10, 270.

^{159.} Fraenkel, G.; Dix, D.T.; Adams, D.G. Tetrahedron Lett. 1964, 3155.

^{160. (}a) Hölzer, B.; Hoffmann, R.W. Chem. Commun. 2003, 732. See also (b) Hoffmann, R.W.; Hölzer, B.; Knopff, O.; Harms, K. Angew. Chem. Int. Ed. 2000, 39, 3072.

 ⁽a) Tamao, K.; Hiyama, T.; Negishi, E.-i. J. Organomet. Chem. 2002, 653, 1; (b) Corriu, R.J.P.; Masse, J.P. J. Chem. Soc. Chem. Commun. 1972, 144a; (c) Tamao, K.; Sumitani, K.; Kumada, M. J. Am. Chem. Soc. 1972, 94, 4374; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 386-387.

^{162.} Morrison, J.D.; Mosher, H.S. Asymmetric Organic Reactions, ACS, Washington, 1976, pp 414-415.

carbon dioxide to give the corresponding carboxylic acid with some retention of configuration

(14% ee) in 38% yield.¹⁶³ The % ee can be as high as 80%, however, when the reactions are carried out in ether.¹⁶³ Better selectivity was observed with menthol-based Grignard reagents.¹⁶⁴ Cyclopropyl derivatives tend to give better selectivity than acyclic or larger ring Grignard reagents. α -Halo-Grignard reagents have been shown to be excellent precursor to chiral Grignard reagents. Hoffmann showed that ethylmagnesium chloride reacted with α -halosulfoxide 145 to give 146, along with 4-chloropenyl ethyl sulfoxide.¹⁶⁵ When 146 was treated with more ethylmagnesium chloride between -50 to -30°C, Grignard reagent 147 was formed in solution. When this reacted with phenylisothiocyanate, thioamide 148 was isolated in 56% yield and 83% ee. Hoffmann observed that racemization of the Grignard reagent 147¹⁶⁶ was slowest in the presence of chloride, an anion of low nucleophilicity. The use of ethylmagnesium chloride was important because the reaction was least complicated by formation of a rearranged Grignard product.¹⁶⁷



When a α -halo Grignard reagent is treated with another organometallic reagent (such as another Grignard reagent), a new Grignard reagent is generated by a carbon-carbon bond-forming reaction.¹⁶⁷ *This appears to be a rearrangement product, but actually arises by formation of a carbonoid species* (sec. 13.8.D) that undergoes a C–H insertion reaction. Reaction of diiodide **149** with isopropylmagnesium chloride, for example, generated the iodo-Grignard reagent **150** at -78° C. As **150** warmed up, it reacted with additional isopropylmagnesium chloride to give

^{163.} Walborsky, H.M.; Impastato, F.J.; Young, A.E. J. Am. Chem. Soc. 1964, 86, 3283.

 ^{164. (}a) Tanaka, M.; Ogata, I. *Bull. Chem. Soc. Jpn.* 1975, 48, 1094; (b) Schumann, H.; Wassermann, B.C.; Hahn, F.E. *Organometallics* 1992, 11, 2803; (c) Dakternieks, D.; Dunn, K.; Henry, D.J.; Schiesser, C.H.; Tiekink, E.R. *Organometallics* 1999, 18, 3342.

^{165.} Hoffmann, R.W.; Hölzer, B.; Knopff, O.; Harms, K. Angew. Chem. Int. Ed. 2000, 39, 3072.

^{166.} Hoffmann, R.W.; Nell, P.; Leo, R.; Harms, K. Chem. Eur. J. 2000, 6, 3359.

^{167.} Hoffmann, R.W.; Knopff, O.; Kusche, A. Angew. Chem. Int. Ed. 2000, 39, 1462.

151, and quenching with methanol gave the observed product **152**.¹⁶⁷ For most of the reactions listed in this section, such carbenoid reactions should not be a major problem.



8.4.F.ii. Diastereoselectivity and Enantioselectivity. Reaction of a Grignard reagent reacts with unsymmetrical ketones or aldehydes that contain a prochiral carbonyl carbon, leads to a new stereogenic center. Diastereomers result if another stereogenic center is present in either the Grignard reagent (but not at the carbon bearing the Mg) or the carbonyl substrate. If 2-pentanone reacts with the Grignard reagent derived from 3-phenyl-1-bromobutane (153), the resulting alcohol will be a mixture of syn and anti diastereomers (154 and 155, respectively). Each diastereomer will be racemic. In light of the previous discussion in section 8.4.F.i., it may be possible for one diastereomer to predominate (the reaction would be diastereoselective) but it should not be enantioselective.



The products from such reactions can be organized into four categories that reflect simple combinations of chiral and achiral Grignard reagents reacting with chiral or achiral carbonyl derivatives. (1) Mixing an achiral Grignard reagent and a carbonyl derivative that does not possess a substituent attached to a stereogenic center generates one new stereogenic center. (2) Mixing a chiral Grignard reagent and a carbonyl derivative that does not possess a substituent attached to a stereogenic center generates diastereomers. (3) Mixing an achiral Grignard reagent and a carbonyl derivative that has a substituent attached to a stereogenic center leads to diastereomers, with possible diastereoselectivity. (4) Mixing a chiral Grignard reagent with a carbonyl derivative that has a substituent attached to a stereogenic center will lead to good diastereoselectivity.

If there is steric bias in a molecule, and if the addition of a Grignard reagent generates diastereomers, the products may be formed with good diastereoselectivity. The rationale for diastereoselectivity discussed in section 4.8 for reduction generally applies to reaction of Grignard reagents and carbonyl derivatives. In a synthesis of vinigrol, by Paquette and co-workers,¹⁶⁸ ketone **156** reacted with vinylmagnesium chloride to give 54% of **157** and 24% of **158**. The observed diastereoselectivity is typical of the exo-selectivity observed similar bicyclic systems (sec. 1.4.E).¹⁶⁹

^{168.} Paquette, L.A.; Guevel, R.; Sakamoto, S.; Kim, I.H.; Crawford, J. J. Org. Chem. 2003, 68, 6096.

^{169. (}a) Jung, M.E.; Hudspeth, J.P. J. Am. Chem. Soc. 1980, 102, 2463; (b) Idem Ibid. 1978, 100, 4309.



MOLECULAR MODELING: Stereochemistry of Vinyl Magnesium Bromide Additions

One synthetic route to vinegrol involves addition of vinyl magnesium bromide to **156**. This occurs from the *exo* carbonyl face (leading to **157**) rather than from the *endo* carbonyl face (leading to **158**). Remember that the addition of nucleophiles to the carbonyl carbon must approach from an angle of 110° (the "Bürgi-Dunitz trajectory"). This fact must be considered when determining the preferred face for reaction, and any possible steric hindrance to that addition.

Examine a space-filling model of **156** (left). Assume that the Grignard reagent approaches from either (*a*) or (*b*), and determine if both *exo* and *endo* faces accessible to the reagent? Is there a clear steric preference for addition to one over the other? Next, examine the LUMO map for **156** (right). This maps the (absolute) value of the lowest-unoccupied molecular orbital onto an electron density surface, which like a space-filling model, indicates overall molecular size and shape. By convention, regions on the surface where the LUMO is most concentrated are colored "blue", while those where it is absent are colored "red". The reagent (a nucleophile) should prefer to attack **156** on the face with the greatest blue area. Does the LUMO map show a clear preference for attack? If it does, which product (**157** or **158**) should result? Note that the LUMO map is provided as a transparent model to allow you to see the underlying structure. You can change it to a solid model (making comparison of the *exo* and *endo* faces easier), by clicking on the map and selecting *Solid* from the **Style** menu at the bottom of the screen.

Good diastereoselectivity can be observed in less sterically demanding systems for selected Grignard reagents. Hoffmann reported good diastereoselectivity when α -haloalkyl Grignard reagents reacted with benzaldehyde.¹⁷⁰ Grignard reagent **159**, for example, gave an 82% yield of **160** + **161** in a 92:8 ratio, showing the reaction clearly favored the syn diastereomer.



Assuming that Grignard reagent addition to a carbonyl is a diastereoselective reaction that produces racemic products, it is important to ask if it is possible for the reaction to be

^{170.} Schulze, V.; Nell, P.G.; Burton, A.; Hoffmann, R.W. J. Org. Chem. 2003, 68, 4546.

enantioselective. If we rely on the carbon bearing the magnesium atom, the answer is usually no. If we incorporate a stereogenic center elsewhere in the molecule, however, the relative merits of the four cases listed above must be discussed.



Case 1 involves an achiral Grignard reagent reacting with a prochiral ketone to give a racemic alcohol. Some asymmetric induction¹⁷¹ has been achieved by forming asymmetric complexes of the Grignard reagent with solvents such as (2R, 3R)-(+)-dimethoxybutane.¹⁷² The two oxygens of this chiral ether coordinate with the Grignard reagent to form a monomeric species such as **162**.¹⁶² In **162**, coordination with the oxygens renders the magnesium asymmetric, and reaction with a prochiral ketone will generate

a diastereomeric transition state for the acyl addition¹⁶² so an excess of one enantiomer will result. Since R² in **162** exists as an equilibrating mixture of stereoisomers (see **144** and **145**), complex **162** represents four stereochemically distinct solvated species, not necessarily present in equal amounts, and each can react with a prochiral substrate at different rates.¹⁶² The extent of induced stereoselectivity is generally low, often 2-3%,¹⁶² even in an asymmetric solvent. When phenylmagnesium bromide reacted with 2-octanone in the optically active solvent 2-methyltetrahydrofuran, for example, 2-phenyl-2-octanol was formed in only 11-18% ee.¹⁷³

In some cases, it is possible to form a chiral, nonracemic alcohol from a prochiral ketone and a Grignard reagent, by adding an asymmetric ligand (a chiral additive) to the reaction mixture. This case is differentiated from the reaction of Grignard reagent with a carbonyl species that has a stereogenic center present in the same molecule (case 3 above, a Cram's rule type system: see sec. 4.8.B for a discussion of Cram's rule). Presumably, the Grignard reagent forms a chiral complex with these additives, promoting facial selectivity in the addition reaction with the carbonyl. In work by Nozaki and co-workers, addition of (–)-sparteine (163) to the reaction of ethylmagnesium bromide and benzaldehyde gave (R)-(+)-1-phenyl-1propanol in 15% yield and 22% ee.¹⁷⁴ Under the same conditions, reaction with acetophenone gave racemic 2-phenyl-2-butanol in 11% yield. Seebach and co-workers showed that addition of 164 to benzaldehyde gave 1-phenyl-1-propanol in 6-8% ee.¹⁷⁵ Inch et al. added furanose 165¹⁷⁶ to a mixture of methylmagnesium bromide and 1-phenyl-1-heptanone, and obtained a 95% yield of (R)-(+)-2-phenyl-2-octanol with 70% ee. Under similar conditions, however, ethylmagnesium bromide reacted with acetophenone to give a 48% yield of (S)-(–)-2-phenyl-

^{171.} Solladie, G. in Asymmetric Synthesis Vol. 2, Morrison, J.D. (Ed.), Academic Press, New York, 1983, pp 157-183.

^{172. (}a) Cohen, H.L.; Wright, G.F. J. Org. Chem. 1953, 18, 432; (b) Allentoff, N.; Wright, G.F. Ibid. 1957, 22, 1.

^{173.} Iffland, D.C.; Davis, J.E. J. Org. Chem. 1977, 42, 4150.

^{174. (}a) Nozaki, H.; Aratani, T.; Toraya, T.; Noyori, R. *Tetrahedron* **1971**, *27*, 905; (b) Nozaki, H.; Aratani, T.; Toraya, T. *Tetrahedron Lett.* **1968**, 4097.

 ^{175. (}a) Seebach, D.; Langer, W. Helv. Chim. Acta 1979, 62, 1701; (b) Seebach, D.; Crass, G.; Wilka, E.-M.; Hilvert, D.; Brunner, E. Ibid. 1979, 62, 2695.

^{176.} Inch, T.D.; Lewis, G.J.; Swainsbury, G.L.; Sellers, D.J. Tetrahedron Lett. 1969, 3657.

2-butanol with 27% ee.¹⁷⁶ Chiral amino alcohols were used as additives by Battioni and Chodkiewicz, but gave optical yields of only 0-20%.¹⁷⁷ Mukaiyama and co-workers obtained good results with the chiral ligand **166** in reactions of organolithium, dialkylmagnesium and Grignard reagents with benzaldehyde.¹⁷⁸ When **166** was added to the reaction, the optical yield of alcohol **167** depended on both the solvent and the temperature of the reaction. In case (2), the stereogenic center of the Grignard might be expected to give some selectivity for the syn or anti diastereomeric product. The configurational instability of the C-Mg bond^{158,159,162} at the putative stereogenic carbon, however, leads to an equilibrating mixture that is effectively a chiral, racemic Grignard reagent, with poor syn-anti selectivity in the diastereomeric alcohol mixture.



If the carbonyl partner contains a stereogenic carbon, as in case (3), the asymmetry of that center should exert an influence when the Grignard reagent reacts with the prochiral carbonyl (the faces of the carbonyl are diastereotopic), leading to some diastereoselectivity in the alcohol product. This is the system that formed the basis of the Cram model,¹⁷⁹ the Cornforth model,¹⁸⁰ the Felkin-Anh model¹⁸¹ and the Karabatsos model¹⁸² discussed in Section 4.8.B. The Cram model, the Cram chelation model or the Felkin-Anh model are generally used to predict selectivity in addition of Grignard reagents to a prochiral carbonyl with stereogenic α - or β - carbons. The presence of a stereogenic center in one of the reactive partners induces facial bias on approach of the two reagents, leading to moderate to good diastereoselection for either the syn or the anti isomer. Examples taken from Mosher and Morrison's compilation are

- 181. Cherest, M.; Felkin, H.; Prudent, N. Tetrahedron Lett. 1968, 2199.
- 182. Karabatsos, G.J. J. Am. Chem. Soc. 1967, 89, 1367.

^{177.} Battioni, J.P.; Chodkiewicz, W. Bull. Soc. Chim. Fr. 1972, 2068.

⁽a) Mukaiyama, T.; Soai, K.; Sato, T.; Shimizu, H.; Suzuki, K. J. Am. Chem. Soc. 1979, 101, 1455; (b) Soai, K.; Mukaiyama, T. Chem. Lett. 1978, 491; (c) Sato, T.; Soai, K.; Suzuki, K.; Mukaiyama, T. Ibid. 1978, 601; (d) Mukaiyama, T.; Suzuki, K.; Soai, K.; Sato, T. Chem. Lett. 1979, 447.

^{179. (}a) Cram, D.J.; Abd Elhafez, F.A J. Am. Chem. Soc. 1952, 74, 5828; (b) Cram, D.J.; Kopecky, K.R. Ibid. 1959, 81, 2748.

^{180.} Cornforth, J.W.; Cornforth, R.H.; Mathew, K.K. J. Chem. Soc. 1959, 112.

shown in Table 8.6,¹⁸³ and Cram's open chain model predicts the diastereoselectivity of case (3) reactions. In Table 8.6, ketone **168** reacted with various Grignard reagents (R^2MgX) to give a mixture of diastereomeric alcohols, **169** and **170**. When the LUMO map (see sec. 4.7.B) for **168** ($R_s = H$, $R_M = Me$, $R_L = Ph$, $R^1 = H$) is prepared, the blue intensity about the carbonyl carbon indicates a preference for **169**.

]		R^1 R^2	MgX►	$\begin{array}{c} R_{M} & OH \\ R_{S} \xrightarrow{\overline{}} R_{L} & R^{1} \\ \hline R_{L} & R^{1} \\ \hline 169 \end{array}$	+	$\begin{array}{c} R_{\rm M} & R^2 \\ R_{\rm S} & \overbrace{\overline{}}^{R_{\rm M}} OH \\ R_{\rm L} & R^1 \\ 170 \end{array}$
<u>R</u> s	<u>R</u> M	$\underline{\mathbf{R}}_{\mathbf{L}}$	<u>R</u> ¹	$\underline{\mathbf{R}}^2$	<u>X</u>	<u> 169 : 170</u>
Н	Me	Ph	Н	Me	Br	2.4 : 1
				Me	Ι	2.0:1
				Et	Br	3.0:1
				Ph	Br	>4.0:1
Н	<i>i</i> -Pr	Ph	Н	<i>i</i> -Pr	Br	1.9 : 1
Me	Et	Ph	Н	Ph	Br	2.9:1
Н	Et	Ph	Н	Me	Ι	2.5:1
				Et	Br	3.0:1
Н	Me	Et	Н	Me	Br	1.5 : 1
Н	Me	Et	Me	Me ₂ CHCH ₂	Br	1.8 : 1
[Reprinted by courtesy of Professor James D. Morrison from Morrison, J.D.; Mosher, H.S. <i>Asymmetric Organic Reactions</i> , American Chemical Society, Washington, D.C. 1976 , pp. 92-93.]						

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As discussed in Chapter 4, the Cornforth dipolar model (sec. 4.7.B) is better able to predict the stereoselectivity for reactions of α -chloroketones, and the Cram cyclic (chelation) model (171)¹⁸⁴ is preferred for reactions of ketones that have heteroatoms in the α -position. The chelation model is very common in Grignard reactions, and it assumes that the magnesium is coordinated to both the heteroatom and the carbonyl oxygen as shown in 171. For this reason, coordination of an organometallic with carbonyls that have a heteroatom in

the α - and β - positions has been termed **chelation control** when it results in formation of products with high diastereoselectivity.¹⁸⁵ Part of this model assumes that the incoming group in **171** (R attached to magnesium) is delivered from the less hindered face (over the smallest group, R_s). In this model, the R¹ group could be H or alkyl. An example of chelation control is the reaction of α -benzyloxy ketone (**172**) with vinylmagnesium bromide, a key step in the Williams and White synthesis of (±)-citreoviridin.¹⁸⁶ In this case, diastereomer **174** was formed exclusively, and the chelated model (**173**) predicted the observed stereochemistry.

^{183.} Reference 162, pp 92-93.

^{184. (}a) Reference 162, pp 94-98; (b) Cram, D.J.; Wilson, D.R. J. Am. Chem. Soc. 1963, 85, 1245.

^{185.} Still, W.C.; Schneider, J.A. Tetrahedron Lett. 1980, 21, 1035.

^{186.} Williams, D.R.; White, F.H. J. Org. Chem. 1987, 52, 5067.



Case (4) from above should give the best diastereoselectivity. The instability of the C-Mg bond, however, leads to poor diastereoselectivity for the carbon bearing the magnesium as observed in case (2). The stereogenic center on the carbonyl substrate remains intact, and it influences the reaction, leading to good diastereoselectivity in the alcohol product upon reaction with a prochiral carbonyl derivative. For all practical purposes this is a case (3) situation, except that there is loss of diastereoselectivity due to the inability to control the configuration of the stereogenic center in the Grignard reagent.

8.4.F.iii. Stereochemical Integrity of Alkenyl Grignard Reagents. A different stereochemical problem arises when vinylmagnesium halides are formed from alkenyl halides. Both (E) and (Z) isomers can be formed. Reaction of stereochemically pure (E) or (Z) alkenyl halides with magnesium gave a mixture of (E) and (Z) vinyl Grignard reagents.¹⁸⁷ Subsequent reaction with carbonyl derivatives gives an allylic alcohol product as an E/Z mixture. Martin et al.¹⁸⁷ reported that reaction of pure (E)- or (Z)-1-bromo-1-alkenes with magnesium metal and then with CO₂ gave stereospecific conversion to the corresponding acid. Although (E) halide gave mainly the (E) product, this is *misleading*. In fact, severe loss of stereochemical integrity was observed and a mixture of both (E) and (Z) isomers was always obtained, as shown in Table 8.7.¹⁸⁸ It is important to note that there are significant differences between the stereochemical ratio of the Grignard reagent and that of the acid product. Table 8.7 shows a comparison of bromopropenes and bromohexenes, where loss of stereochemical integrity is more pronounced in the longer chain alkenes. In addition, greater loss of stereochemical integrity is apparent upon reaction with the electrophile (CO₂). A partial solution to this problem is reaction of the vinyl Grignard reagent with alkyl halides in the presence of cuprous iodide [Cu(I)I], which does little for the initial loss of stereochemistry upon formation of the Grignard, but in subsequent reactions, greater retention of stereochemistry is observed.¹⁸⁹ An example is the reaction of **175** with iodopropane in the presence of cuprous iodide, giving a 97% vield of **176**. The original 90:10 (Z/E) mixture in 175 was retained (88:12 Z/E) in the final product 176.

$$(Z/E = 90:10) \qquad \underbrace{1. n-C_{3}H_{7}-I, CuI, THF, -30^{\circ}C}_{175} \qquad \underbrace{1. n-C_{3}H_{7}-I, CuI, THF, -30^{\circ}C}_{176} \qquad (Z/E = 88:12)$$

^{187.} Martin, G.J.; Mèchin, B.; Martin, M.L. C.R. Acad. Sci. Ser. C 1968, 267, 986.

^{188.} Martin, G.J.; Martin, M.L. Bull. Soc. Chim. Fr. 1966, 1636.

^{189.} Derguini-Boumechal, F.; Linstrumelle, G. Tetrahedron Lett. 1976, 3225.

Table 8.7.Stereoselectivity in the Formation of Grignard Reagents from Stereo-
chemically Pure Vinyl Halides and Subsequent Reaction with CO2

Halide	(<u>Z : E)</u>	<u>RMgBr (Z : E)</u>	<u>RCOOH (Z : E)</u>
(Z)-1-Bromo-1-propene	98.5:1	80-90 : 20-10	85-95 : undetected
(E)-1-Bromo-1-propene	5:95	30-40 : 70-60	15-5 : 85-95
(Z)-1-Bromo-1-hexene	97:1	75-85 : 25-15	45-55 : 55-45
(E)-1-Bromo-1-hexene	1:99	40-50 : 60-80	35-45 : 65-55

Another problem arises with allylic Grignard reagents. When the magnesium halides derived from (E)-1-bromo-2-butene were quenched with water (see Table 8.8),¹⁹⁰ the double bond had isomerized and a mixture of 1-butene, (Z)-2-butene and (E)-2-butene was obtained. This allylic rearrangement is well known in reactions of Grignard reagents.¹⁹¹ Increasing the solvating power of the solvent, as in changing from diethyl ether to THF, increased the lability of the C–Mg bond and gave more isomerization.

Table 8.8. Isomerization of Crotylmagnesium Halides

<u>Crotyl-MgX (X)</u>	<u>Solvent</u>	<u>1-Butene</u>	(<u>Z)-2-Butene</u>	(<u>E)-2-Butene</u>
Br	ether	75	11	14
Cl	ether	80	9	11
Ι	ether	80	10	10
Cl	THF	60	15	25
Ι	THF	55	20	25

Reaction of an allylic magnesium halide with an electrophile can give a new bond at either carbon of the allylic carbanion, so two isomeric products are possible.¹⁹² Felkin and co-workers described the reaction with ketones as a non-cyclic S_E2' rearrangement, and it is sensitive to steric encumbrance at the carbonyl carbon.¹⁹³ Allylic Grignard reagent 177, when generated from either the (*E*)- or the (*Z*)- bromide, formed an equilibrating mixture (177 and 180). When this mixture of Grignard reagents reacted with a ketone (via 178 and 181, respectively), isomeric alcohols 179 and 182 were formed. Increasing the steric bulk of R¹ and R destabilizes 178 relative to 181, favoring 182 over 179. The 2-butenyl derivative (R¹ = Me) reacted primarily as the crotyl derivative (177),¹⁹⁴ but 177 was in equilibrium with a small amount of 180.¹⁹⁵

^{190.} Agami, C.; Andrac-Taussig, M.; Prévost, C. Bull. Soc. Chim. Fr. 1966, 1915.

^{191.} Agami, C. Bull. Soc. Chim. Fr. 1967, 4031.

^{192.} Hoffmann, R.W. Angew. Chem. Int. Ed. 1982, 21, 555.

^{193.} Chérest, M.; Felkin, H.; Frajerman, C. Tetrahedron Lett. 1971, 379.

^{194.} Gaudemar, M. Bull. Soc. Chim. Fr. 1958, 1475.

^{195.} Nordlander, J.E.; Young, W.G.; Roberts, J.D. J. Am. Chem. Soc. 1961, 83, 494.



When 177/180 reacted with aldehydes¹⁹⁶ or unhindered ketones,¹⁹⁷ α -methallyl alcohol 179 was formed (182/179 ratio is < 0.01). With diisopropyl ketone (R = *i*-Pr) the 182/179 ratio was 0.5¹⁹⁸ and with di-*tert*-butyl ketone 182 was the major product.^{198a,199} *tert*-Butylalkylmagnesium bromide (R¹ = *t*-Bu)¹⁹⁴ increased the strain in 178 to the extent that even the unhindered substrate acetone gave predominantly 182 (R = Me), although similar reaction with acetaldehyde gave only 179 (182179 ratio is <0.01). In all cases 182 was isolated predominantly as the (*E*) isomer [(*E*/*Z*) ratio is > 20:1]. Cyclic ketones such as cyclopentanone showed the greatest selectivity for 182 [cyclopentanone: 182:179 = 65:1, R = R¹ = -(CH₂)₄-] and cyclohexanone gave a 3:1 ratio (R=R¹ = -(CH₂)₅-). Miginiac, Prévost and co-workers noted that 1-bromo-2-pentene reacted with magnesium and various electrophiles to give primarily the 3-alkyl derivatives.²⁰⁰ A minor side reaction is sometimes observed when attempting to prepare the Grignard reagent of a ω -haloalkene. The Grignard reagent derived from reaction of 6-bromo-1-hexene and magnesium gave ~ 5% of 1-methylcyclopentane via addition of the Grignard reagent to the alkene double bond.²⁰¹ The analogous organolithium reagents can give excellent yields of cyclization under similar conditions (RX + Li°), as discussed in Section 8.5.F.ii.

8.4.G. Reduction, Organocerium Reagents, and Enolization

8.4.G.i. Reduction. Although Grignard reagents react with ketones and aldehydes to give alcohols in good yield, there are a few reactions that compete with the normal reactions. Two common side-reactions are reduction and enolization. Reduction of carbonyl compounds occur when the carbonyl unit and the magnesium-bearing carbon of the Grignard reagent are sterically

^{196.} Oh, Kiun-Houo Ann. Chim (Fr.) 1940, 13, 175.

^{197.} Roberts, J.D.; Young, W.G. J. Am. Chem. Soc. 1945, 67, 148.

 ⁽a) Benkeser, R.A.; Young, W.G.; Broxterman, W.E.; Jones, Jr., D.A.; Piaseczynski, S.J. J. Am. Chem. Soc. 1969, 91, 132; (b) Young, W.G. Roberts, J.D. Ibid. 1945, 67, 319; (c) Gross, B.; Prevost, C. Bull Soc. Chim. Fr. 1967, 3610.

^{199.} Footnote 6 in Benkeser, R.A.; Broxterman, W.E. J. Am. Chem. Soc. 1969, 91, 5162.

^{200.} Miginiac-Groizeleau, L.; Miginiac, P.; Prévost, C. Compt. Rend. 1965, 260, 1442.

^{201.} Drozd, V.N.; Ustynyuk, Yu.A.; Tsel'eva, M.A.; Dmitriev, L.B. Zh. Obshch. Khim. 1969, 39, 1991 (Engl., p1951).

hindered,²⁰² and the Grignard reagent must possess a β -hydrogen. Reaction of **183** with *tert*butylmagnesium chloride, for example, gave >90% of the reduction product, alcohol **185** with none of the carbonyl addition product.²⁰³ The reduction is thought to proceed by a coordination complex that leads to a transition state close to **184**, which is similar to the transition state observed in the **Meerwein-Ponndorf-Verley reduction**²⁰⁴ (sec. 4.10.J) and the **Oppenauer oxidation** (sec. 3.2.E). Coordination between the carbonyl oxygen and magnesium leads to complex **184**, where hydrogen transfer gives the alcohol **185**, accompanied by elimination of H and MgX from the Grignard to give an alkene (in this case isobutylene). Hamelin^{203b} showed that even an unhindered aldehyde such as propanal can be reduced with a small Grignard reagent such as ethylmagnesium bromide. A Grignard reaction between hindered ketones and aldehydes often leads to reduction as a synthetically useful process. Camphor (**186**) is reduced to borneol (**187**) and isoborneol (**188**) upon reaction with Grignard reagents, with selectivity for isoborneol as seen in Table 8.9.²⁰⁵



 Table 8.9.
 Reduction of Camphor with Grignard Reagents

0 RMgX	н 187 ^{ОН}	+ , OH 188 H
<u>RMgX</u>	<u>% 187</u>	<u>% 188</u>
EtMgBr	35	29
EtMgBr <i>i</i> -PrMgBr	35 45	29 45
EtMgBr <i>i</i> -PrMgBr <i>n</i> -PrMgBr	35 45 34	29 45 48

Varying degrees of asymmetric induction can be achieved in the reduction process when chiral Grignard reagents and asymmetric solvents are employed.²⁰⁶ In most cases, the %

- 203. (a) Whitmore, F.C.; Whitaker, J.S.; Mosher, W.A.; Breivik, O.N.; Wheeler, W.R.; Miner, Jr., C.S.; Sutherland, L.H.; Wagner, R.B.; Clapper, T.W.; Lewis, C.E.; Lux, A.R.; Popkin, A.H. J. Am. Chem. Soc. 1941, 63, 643; (b) Hamelin, A. Bull. Soc. Chim. Fr. 1961, 926.
- 204. (a) Meerwein, H.; Schmidt, R. Ann. 1925, 444, 221; (b) Ponndorf, W. Angew. Chem. 1926, 39, 138; (c) Verley, A. Bull. Soc. Chim. Fr. 1925, 37, 537, 871; (d) Wilds, A.L. Org. React. 1944, 2, 178.
- 205. Malkonen, P.J. Suomen Kemistilehti 1965, 38B, 89 [Chem. Abstr. 63: 8411b 1965].
- 206. (a) Birtwistle, J.S.; Lee, K.; Morrison, J.D.; Sanderson, W.A.; Mosher, H.S. *J. Org. Chem.* **1964**, *29*, 37 and references cited therein; (b) Reference 162, pp 177-202.

^{202.} Reference 83, p 138.

ee for reduction is small. Nasipuri and coworkers²⁰⁷ described the asymmetric reduction of phenylalkyl ketones.²⁰⁸ A cyclic model²⁰⁹ and an acyclic model²¹⁰ were proposed. Asymmetric induction was higher with phenylalkyl ketones than with cyclohexylalkyl ketones or *tert*-butylalkyl ketones.²¹¹

Since the Grignard reduction can be used synthetically, the appropriate functional group transform is



8.4.G.ii. Organocerium Reagents. Reduction in Grignard reactions of hindered ketones can severely limit a carbonyl alkylation reaction. This limitation can be circumvented, however, by the converting the Grignard reagent to an organocerium reagent. Imamoto and coworkers showed that methyl mesityl ketone (190) gave only 10% of the acyl addition product (191) upon reaction with butylmagnesium bromide.²¹² Organocerium 189, formed by the reaction of butylmagnesium bromide and cerium chloride (CeCl₃), reacted with 190 to give a 57% yield of 191²¹² A synthetic example using an organocerium reagent is taken from Majetich and Zhang's synthesis of perovskone, in which sterically hindered ketone 192 reacted with the organocerium reagent derived from vinylmagnesium bromide to give the 1,2-addition product 193.²¹³ In this example, mild acid hydrolysis led to elimination of water and formation of the extended conjugated ketone 194 in an overall yield of 90%.



^{207.} Nasipuri, D.; Ghosh, C.K.; Mukherjee, P.R.; Venkataraman S. *Tetrahedron Lett.* **1971**, 1587 and references cited therein.

- 208. Reference 162, pp 182-187.
- 209. Mathieu, J.; Weill-Raynal, J. Bull. Soc. Chim. Fr. 1968, 1211.
- 210. Cabaret, D.; Welvart, Z. Chem. Commun. 1970, 1064.
- 211. Morrison, J.D. Survey of Progress in Chemistry, Vol. 3, Academic Press, New York, 1966, p 147.
- (a) Imamoto, T.; Sugiura, Y.; Takiyama, N. *Tetrahedron Lett.* 1984, 25, 4233; (b) Imamoto, T.; Sugiura, Y. J. Organomet. Chem. 1985, 285, C21; (c) Imamoto, T.; Takiyama, N.; Nakamura, K *Tetrahedron Lett.* 1985, 26, 4763.
- 213. Majetich, G.; Zhang, Y. J. Am. Chem. Soc. 1994, 116, 4979.



Organolithium reagents (sec. 8.5) are also useful precursors. Vinylcerium reagent **196** was prepared from vinyl bromide **195**, in Ovaska and Roses' synthesis of fused polycyclic ring systems.²¹⁴ When **196** reacted with the cyclopentanone derivative shown, alcohol **197** was isolated in 61% yield after hydrolysis.



 Table 8.10. Competition for Nucleophilic Addition, Reduction, and Enolate Formation in Reactions of Diisopropyl Ketone with Grignard Reagents

	RMgX H ₂ O	o ⁻ enol + 、	OH + reduction +	O^{-} R addition
RMgX	RMgX/Ketone	% Enolate	% Reduction	% Addition
EtMgBr	1.3	1	21	78
	1.5	1	19	80
	2.5	1	15	80
	1.2	2	21	77
n-PrMgCl	1.2	2	51	46
. 8-	2.5	1	37	62
<i>n</i> -PrMgBr	1.2	1	64	35
. 8	1.4	2	60	36
n-PrMgI	1.2	2	69	30
<i>i</i> -PrMgCl	1.2	28	72	0
<i>i</i> -PrMgBr	12	29	65	0
	1.4	30	65	ŏ
<i>i</i> -PrMgI	1.4	30	70	0
[Reprinted with permission from Cowan, D.O.; Mosher, H.S. J. Org. Chem. 1962, 27, 1. Copyright © 1962 American Chemical Society.]				

8.4.G.iii. Enolization. Aldehydes and ketones have acidic protons on the α -carbon, which can be removed by the basic Grignard reagent to generate an enolate anion (sec. 9.2.A). Formation

^{214.} Ovaska, T.V.; Roses, J.B. Org. Lett. 2000, 2, 2361.

of the enolate anion can sometimes compete with nucleophilic addition to the carbonyl. If there are no secondary reactions, hydrolysis of the enolate product regenerates the starting ketone and the net result is isolation of the starting material. Nucleophilic addition to the carbonyl is usually faster than deprotonation, but small amounts of enolization can be observed as shown in Table 8.10 for diisopropyl ketone (**198**).²¹⁵ With unhindered Grignard reagents, the amount of enolate anion formed is insignificant, and reduction is the major reaction that competes with nucleophilic addition. With the hindered isopropylmagnesium halide, steric interactions completely suppressed addition, and reduction accounted for 69% of products with only 2% enolization. Hamelin observed similar reactivity in reactions with ethylmagnesium bromide,²¹⁶ in which the effect of solvent and temperature on reduction and enolization was probed. Increasing the size of the groups attached to the carbonyl increased the amount of reduction but only slightly increased the amount of enolization. Increasing the size of the groups attached to the carbonyl increased enolate formation.

8.5. ORGANOLITHIUM REAGENTS (C-Li)

Grignard reagents are clearly important in synthesis. If MgX is replaced with Li, another class of organometallic reagents is available, the organolithium reagents. Organolithium reagents are also potent nucleophiles and they are more basic than Grignard reagents. Both features can be exploited in synthesis.²¹⁷

8.5.A. Preparation, Structure, and Stability

Organolithium reagents, characterized by a C-Li bond, are as important in organic synthesis as the Grignard reagents. Lithium is less electronegative than carbon, and the carbon of the C-Li bond is polarized δ -, as in Grignard reagents.²¹⁸ Organolithium reagents are expected to behave both as a nucleophile and as a base. It is important to understand the chemical properties of organolithium reagents, and to note differences with Grignard reagents before discussing their reactions.²¹⁹

Ethyllithium was discovered by Schlenk and Holtz in 1917,²²⁰ but it was not until 1930²²¹ that Ziegler and Colonius discovered that organolithium reagents could be prepared by direct

^{215.} Cowan, D.O.; Mosher, H.S. J. Org. Chem. 1962, 27, 1.

^{216.} Hamelin, R. Bull Soc. Chim. Fr. 1961, 915 and references cited therein.

^{217.} Organolithiums in Enantioselective Synthesis (Series: Topics in Organometallic Chemistry, Vol. 5), Hodgson, D.M. (Ed.), Springer Verlag, Heidelberg, 2003.

 ⁽a) Wakefield, B.J. *The Chemistry of Organolithium Compounds*, Pergamon Press, Oxford, 1974; (b) Clayden, J. Organolithiums: Selectivity for Synthesis, Pergamon, Amsterdam, The Netherlands, 2002.

^{219.} Mallan, J.M.; Bebb, R.L. Chem. Rev. 1969, 69, 693.

^{220.} Schlenk, W.; Holtz, J. Berichte 1917, 50, 262.

^{221.} Ziegler, K.; Colonius, H. Annalen 1930, 479, 135.

reaction of lithium metal and an alkyl halide,²²² as in the reaction of lithium and chlorobutane to give *n*-butyllithium (CH₃CH₂CH₂CH₂Li, or BuLi). Other halides can be used, as seen by the conversion of chloride **199** to **200**, taken from a synthesis of (–)-frontalin by Yus and coworkers.²²³ The naphthalene added to this reaction may assist formation of **200** via formation of lithium naphthalenide. Two years prior to the work of Ziegler and Colonius, Schlenk and Bergmann had reported that ethyllithium (CH₃CH₂Li, or EtLi) reacted with fluorene (**201**), with exchange of the acidic hydrogen with Li to give fluorenyllithium (**202**).²²⁴ These two reactions (lithium-halogen exchange, and lithium-hydrogen exchange) describe the main methods for preparing organolithium reagents and the latter also describes the most useful synthetic application, removal of an acidic hydrogen to generate a new organolithium species.



Organolithium reagents are usually written as R–Li, but this simple representation does not begin to describe their actual structure.^{219,222,225} Some physical data²²² suggest that the C–Li bond in an organolithium is highly covalent. It is known that organolithium reagents exist as associated aggregates, due in part to this covalent character. Both methyllithium²²⁶ and ethyllithium²²⁷ have been obtained in crystalline form and their crystal structure determined by X-ray crystallography. The structure in Figure 8.1²²⁸ is that of crystalline isopropyllithium reported by Siemeling and co-workers, which exists as a hexamer, (*i*-PrLi)₆. The X-ray crystal structure of 9,9-dilithiofluorene has also been reported,²²⁹ the first for a dilithiated hydrocarbon.



Figure 8.1. X-ray crystal structure of isopropyllithium (hydrogen atoms are hidden for clarity). [Reprinted with permission from Siemeling, U.; Redecker, T.; Neumann, B.; Stammler, H.-G. J. Am. Chem. Soc. 1994, 116, 5507. Copyright © 1994 American Chemical Society.] Drawn with Spartan software, Wavefunction, Inc. Hydrogen atoms omitted for clarity.

- 222. Deberitz, J. Janssen Chimica Acta 1984, 2, 3.
- 223. Yus, M.; Ramón, D.J.; Prieto, O. Eur. J. Org. Chem. 2003, 2745.
- 224. Schlenk, W.; Bergmann, E. Annalen 1928, 463, 1 (see p 98).
- 225. (a) Brown, T.L. Advan. Organomet. Chem. 1965, 3, 365; (b) Brown, J.M. Chem. Ind. (London) 1972, 454.
- 226. Weiss, E.; Lucken, E.A.C. J. Organomet. Chem. 1964, 2, 197.
- 227. Dietrich, H. Acta Cryst. 1963, 16, 681.
- 228. Siemeling, U.; Redecker, T.; Neumann, B.; Stammler, H.-G. J. Am. Chem. Soc. 1994, 116, 5507.
- 229. Linti, G.; Rodig,, A.; Pritzkow, H. Angew. Chem. Int. Ed. 2002, 41, 4503

Methyllithium and ethyllithium are tetrameric in the solid state,^{227,230} and most organolithium reagents are highly associated in solution.^{218a,219} The degree of association is related to the solvent and structure of the organolithium, but tends to be higher for straight-chain than for branched (secondary and tertiary) organolithium reagents. The extent of association of the organolithium is important since it can affect the rate of metal-halogen or metal-hydrogen exchange, as well as the product distribution. Table 8.11^{222,231,225a} shows the degree of association of several common organolithium reagents in various solvents, which decreases as the coordinating ability of the solvent increases. This observation can loosely be compared with increasing solvent polarity. The most commonly used solvents in reactions of organolithium reagents are ether, THF, pentane or hexane.²³² Increased solvation reduces the ability of the organolithium reagent to associate, and thereby form solvated oligomers.²³² Williard and co-workers determined the X-ray structures of butyllithium•TMEDA, •THF, and •DME complexes, and showed that they are tetramers.²³³ Complexing also increases the ionic character of the relatively covalent C-Li bond, lowering the energy requirements for the transition state leading to reactions.²³⁴ (-)-Sparteine is often added to organolithium reagents, and the resulting reagent can lead to asymmetric induction in certain reactions. Strohmann and co-workers determined the X-ray crystal structure of *tert*-butyllithium•(–)-sparteine,²³⁵ which has the monomeric structure **203**.

R−Li → (R−Li) _n					
<u>R</u>	Solvent	<u>n</u>			
Et n-Bu	cyclohexane hexane ether benzene cyclohexane benzene ether	6 6 2 6,2 6 6 6			
<i>n</i> -Bu (+ TMEDA) <i>t</i> -Bu	hexane hexane benzene	1 4 4			
Ph	ether	2			
[Reprinted with permission from Mallan, J.M.; Bebb, R.L. Chem. Rev., 1969, 69, 693. Copyright © 1969 American Chemical Society.]					

 Table 8.11. Association of Organolithium Reagents in Common Solvents

- 230. Dietrich, H. Z. Naturforsch. 1959, 14B, 739.
- 231. (a) Reference 219, p 696; (b) Brown, T.L. Acc. Chem. Res. 1968, 1, 23; (c) West, P.; Waack, R. J. Am. Chem. Soc. 1967, 89, 4395.
- 232. Miginiac-Groizeleau, L. Bull. Soc. Chim. Fr. 1963, 1449.
- 233. Nichols, M.A.; Williard, P.G. J. Am. Chem. Soc. 1993, 115, 1568.
- 234. (a) Waack, R.; Doran, M.A. *Chem. Ind. (London)* **1962**, 1290; (b) Zakharkin, L.I.; Okhlobystin, O. Yu.; Bilevitch, K.A. *Tetrahedron* **1965**, *21*, 881.
- 235. Strohmann, C.; Seibel, T.; Strohfeldt, K. Angew. Chem. Int. Ed. 2003, 42, 4531.



[Reprinted with permission from Strohmann, C.; Seibel, T.; Strohfeldt, K. *Angew. Chem. Int. Ed.* **2003**, 42, 4531. Copyright © **2003** Wiley-VCH Verlag GmbH & Co, KGaA, Weinheim.] Structure drawn with Spartan by Wavefunction, Inc. Hydrogen atoms omitted for clarity.

Although ethers are used as solvents for reactions of organolithium reagents, they also react with them. Ethers are Lewis bases and coordinate to lithium, stabilizing the organometallic reagent and participating in subsequent reactions. In most cases, the ether fragment does not appear in the final product.^{236,218} The α -hydrogen of an ether is readily removed by the basic organolithium reagents, via Li–H exchange (this is an acid-base reaction, and the conjugate acid is an alkane, RLi \rightarrow R–H). Disproportionation of the lithio-ether derivative (**204**) generates an



alkoxide and an alkene when tetrahydrofuran (THF) is the solvent.²³⁷ The acidity of the α -proton varies with the ether and the organolithium reagent. It is not surprising, therefore, that organolithium reagents have different stabilities in different solvents. The half-life of *n*-butyllithium in diethyl ether at 25°C is 153 hours, whereas that of ethyllithium is 54 hours, and that of cyclohexyllithium is 30 minutes.²³⁸ This stability to reaction of *n*-butyllithium can be used as an approximate reaction order for Li–H exchange. Note that the relative stability of organolithium reagents can be determined, based on the tin-lithium exchange equilibrium reaction.²³⁹ Primary organolithium reagents. It has also been determined that *n*-butyllithium decomposes in THF in 2 h at 25°C.²⁴⁰ Stability can be increased by the addition of a less acidic co-solvent such as diethyl ether or tetrahydropyran (THP). Solutions of *n*-butyllithium are

⁽a) Reference 219, p 696; (b) Applequist, D.E. O'Brien, D.F. J. Am. Chem. Soc. 1963, 85, 743; (c) Curtin, D.Y.; Koehl, Jr., W.J. Ibid. 1962, 84, 1967; (d) Eastham, J.F.; Gibson, G.W. J. Org. Chem. 1963, 28, 280; (e) Eastham, J.F.; Gibson, G.W. J. Am. Chem. Soc. 1963, 85, 2171; (f) Mulvaney, J.E.; Gardlund, Z.G.; Gardlund, S.L. Ibid. 1963, 85, 3897; (g) Waack, R.; Doran, M.A.; Stevenson, P.E. J. Organomet. Chem. 1965, 3, 481.

^{237. (}a) Reference 219, p 697; (b) Bartlett, P.D.; Friedman, S.; Stiles, M. J. Am. Chem. Soc. 1953, 75, 1771;
(c) Rembaum, A.; Siao, S.P.; Indictor, N. J. Polymer. Sci., 1962, 56, S17; (d) Gilman, H.; Gaj, B.J. J. Org. Chem. 1957, 22, 1165.

^{238. (}a) Reference 219, pp 697, 716; (b) Seyferth, D.; Cohen, H.M. J. Organomet. Chem. 1963, 1, 15.

^{239.} Graña, P.; Paleo, M.R.; Sardina, F.J. J. Am. Chem. Soc. 2002, 124, 12511.

^{240. (}a) Reference 219, p 716; (b) Gilman, H.; Schwebke, G.L. J. Organomet. Chem. 1965, 4, 483.

stable for 24 hours in an ether-THF mixture, and up to one week in an ether-THP solution.²⁴⁰ Addition of a hydrocarbon cosolvent such as pentane, hexane or cyclohexane to the ether also extends the lifetime of the organolithium reagent. Lowering the temperature of the reaction from 25 to 0 or to -78° C significantly reduces the rate of the cleavage reaction, extending the lifetime of the organolithium in solution, and as noted above the solvent plays a critical role. In DME, the half-life of *tert*-butyllithium is 11 minutes at -70° C but <2 minutes at -40° C, whereas in THF the half life is 338 minutes at -40° C and only 42 minutes at -20° C.²⁴¹ In THF, *n*-butyllithium has a half life of 1039 minutes at 0°C but only 38 minutes at 20°C, and in DME at -20° C the half life is 11 minutes. In ether, however, *n*-butyllithium has a half-life of 9180 minutes (153 hours) at 20°C but 1860 minutes (31 hours) at the reflux temperature of 35°C.²⁴¹ The general reactivity of organolithium reagents in cleavage reactions of diethyl ether via Li-H exchange is²⁴²

The reactivity of organolithium reagents in ethers can be increased by addition of a Lewis base that is stronger than diethyl ether or THF. When dimethoxyethane is used as a solvent, for example, the reactivity is greatly increased.²⁴³ The two oxygens in dimethoxyethane coordinate to the lithium of the organolithium reagent, and generate what is essentially a monomeric

organolithium species (**RLi-DME**). Such coordination may also increase the polarity of the C–Li bond, and thereby the carbanionic character. Similar effects are observed when stoichiometric amounts of nitrogen bases such as DABCO (1,4-diazabicyclo[2.2.2] octane²⁴⁴ and TMEDA^{244,218} are added. Alkoxides



such as potassium *tert*-butoxide have also been used,²⁴⁵ but are less effective. The effects of the additives are apparent in the reaction of benzene with *n*-butyllithium.²⁴⁵ A refluxing solution of *n*-butyllithium in benzene is rather stable, giving < 5% of phenyllithium. Addition of TMEDA, however, led to a 76% yield of phenyllithium (three h at ambient temperatures).²⁴⁵ The structure of a 1:1 complex between allyllithium and TMEDA was determined by NMR at low temperature.²⁴⁶ With unsymmetrical alkyl substitution at the termini, the allyl C–C bond to the more substituted terminus is of higher bond order than to the less substituted terminus.

^{241.} Stanetty, P.; Mihovilovic, M.D. J. Org. Chem. 1997, 62, 1514.

^{242.} Gilman, H.; Haubein, A.H.; Hartzfeld, H. J. Org. Chem. 1954, 19, 1034.

^{243.} Schlosser, M. J. Organomet. Chem. 1967, 8, 9.

^{244.} Reference 222, p 4 and reference 10 therein.

^{245.} Eberhardt, G.G.; Butte, W.A. J. Org. Chem. 1964, 29, 2928.

^{246.} Fraenkel, G.; Qiu, F. J. Am. Chem. Soc. 2000, 122, 12806.

Many of the organolithium reagents used for reactions are commercially available, usually packaged in bulk ether or hydrocarbon solvents and the latter often contains many hydrocarbon impurities. Impurities such as these are not a problem for most applications unless the reaction products are alkanes or alkenes, since many products are isolated by chromatography. If the reagent is allowed to age in an ether solvent, there may be contamination caused by the deprotonation reaction, which reduces the amount of organolithium and also generates alkoxides. Once a bottle of commercial reagent has been opened, it reacts with moisture and oxygen to further reduce the molarity of the solution and generate additional alkoxide. For these reasons organolithium reagents should always be standardized prior to each use. Several methods have been developed for this purpose, each taking advantage of the basicity or complexing ability of the organolithium reagent.

Gilman titration²⁴⁷ gives the total alkali (organolithium + alkoxide) when one aliquot is titrated first with water, and then with standardized HCl. Quenching a second aliquot with benzyl chloride, followed by titration with H₂O and then standardized HCl gives the alkoxide concentration. The difference in these values is the molarity of the organolithium. 1,3-Diphenylacetone tosylhydrazone (A),²⁴⁸ 2,5-dimethoxybenzyl alcohol (**B**)²⁴⁹ and diphenylacetic acid (**C**)²⁵⁰ have all been utilized for standardization, each relying on removal of an acidic proton to generate a colored anion. The use of 1,10-phenanthroline (phen, **D**) as a titration reagent relies on complexation between the organolithium and the two nitrogens, leading to a reversible charge transfer complex that has a distinct color.²⁵¹ Titration with 2-butanol destroys the complex, and the resultant color change allows the molarity to be determined. Salicylaldehyde phenylhydrazone (**E**) has been used as an indicator, where deprotonation of the phenolic OH leads to a yellow alkoxide anion.²⁵² More than one equivalent of the organolithium reagent removes the hydrazone NH to give a red dianion, which is the endpoint for the titration.



^{247. (}a) Gilman, H.; Haubein, A.H. J. Am. Chem. Soc. 1944, 66, 1515; (b) Gilman, H.; Cartledge, F.K. J. Organomet. Chem. 1964, 2, 447.

^{248.} Lipton, M.F.; Sorensen, C.M.; Sadler, A.C.; Shapiro, R.H. J. Organomet. Chem. 1980, 186, 155.

^{249.} Winkle, M.R.; Lansinger, J.M.; Ronald, R.C. J. Chem. Soc. Chem. Commun. 1980, 87.

^{250.} Kofron W.G.; Baclawski, L.M. J. Org. Chem. 1976, 41, 1879.

^{251.} Watson, S.C.; Eastham, J.F. J. Organomet. Chem. 1967, 9, 165.

^{252.} Love, B.E.; Jones, E.G. J. Org. Chem. 1999, 64, 3755.

8.5.B. Metal-Halogen Exchange

For applications where the organolithium reagent is not commercially available, the reagent can be prepared by direct synthesis (by reaction of lithium metal with the appropriate alkyl halide). The reaction between one organolithium reagent and an alkyl halide generates a new organolithium reagent, along with a new halide. This reaction can be used to prepare many reagents that can be used in subsequent reactions. Methods have been reported for the preparation and synthetic use of functionalized aromatic and heteroaromatic organolithium reagents that do **not** rely on deprotonation methods.²⁵³

8.5.B.i. Preparation of Organolithium Reagents. When an alkyl halide reacts with lithium metal, a new organolithium reagent is produced along with a new alkyl halide. This process is an exchange reaction, and it probably proceeds by a one-electron transfer from lithium to the halide as shown.^{218,219} Using highly purified lithium leads to a dramatic decrease in formation of the organolithium reagent,²⁵⁴ and it was discovered that the lithium must contain at least 0.02% of sodium for the reaction to proceed normally.

$$\begin{array}{c} \mathbf{R} - \mathbf{X} \\ + \\ |\mathbf{L}\mathbf{i} - \mathbf{L}\mathbf{i}|_{n} \end{array} \longrightarrow \begin{bmatrix} \mathbf{R}^{-\cdots} \mathbf{X}^{-} \\ |\mathbf{L}\mathbf{i}^{\bullet}|_{n-1} \end{array} \end{bmatrix} \longrightarrow \begin{bmatrix} \mathbf{R}^{\bullet} & \mathbf{X}^{-} \\ |\mathbf{L}\mathbf{i}^{\bullet}|_{n-1} & \mathbf{L}\mathbf{i}^{+} \end{bmatrix}$$

A related and useful process is the **Wittig-Gilman reaction**, in which an organolithium (R'–Li) reacts with an alkyl halide to produce a new organolithium (R–Li) via metal-halogen exchange.²⁵⁵ Several mechanisms have been proposed for this exchange.²⁵⁶ The reaction is reversible, and the equilibrium favors the more stable organolithium reagent. The reactivity of the alkyl halide partner is also important. If R–X is more susceptible to nucleophilic displacement than R¹–X, the reaction proceeds to the right. An alternative view is to recognize that when the p K_a of RH is less than that of R¹H (RH is more acidic than R¹H), R¹H is favored.

 $R - X + R^1 - Li \longrightarrow R - Li + R^1 - X$

Exchange of the newly formed organolithium with the newly formed alkyl halide can lead to a mixture of organolithium reagents.²⁵⁷ Proper choice of the initial halide and the organolithium reagent can usually produce a good yield of the desired organolithium reagent, and minimize

^{253.} Nájera, C.; Sansano, J.M.; Yus, M. Tetrahedron 2003, 59, 9255.

⁽a) Beel, J.A.; Koch, W.G.; Tomasi, G.E.; Hermansen, D.E.; Fleetwood, P. J. Org. Chem. 1959, 24, 2036;
(b) Kamienski, C.W.; Esmay, D.L. Ibid. 1960, 25, 1807; (c) Seyferth, D.; Suzuki, R.; Murphy, C.J.; Sabet, C.R. J. Organomet. Chem. 1964, 2, 431.

^{255. (}a) Jones, R.G.; Gilman, H. Org. React. 1951, 6, 339; (b) Gilman, H.; Langham. W.; Jacoby, A.L. J. Am. Chem. Soc. 1939, 61, 106; (c) Wittig, G.; Pockels, U.; Dröge, H. Chem. Ber. 1938, 71, 1903.

 ⁽a) Schlosser, M. Strukture und Reactivität Polarer Organometallic, Springer-Verlag, New York, 1973, p 187; (b) Russel, G.A.; Lamsun, D.W. J. Am. Chem. Soc. 1969, 91, 3967.

^{257.} Applequist, D.E; O'Brien, D.F. J. Am. Chem. Soc. 1963, 85, 743.

the reverse reaction. This exchange reaction is very rapid when *tert*-butyllithium is used with primary alkyl halides. Bailey showed that *tert*-butyllithium reacted with neopentyl iodide (**205**) in a mixture of pentane and ether, to give **206** in $< 5 \text{ min at } -78^{\circ}\text{C}$.²⁵⁸ In this case, **206** was treated with butanal, to give an 89% yield of alcohol **207** (sec. 8.5.C). It should be noted, however, that this particular reaction gives good results only with primary iodides. Halides that react with the organolithium reagent should generate a new organolithium that is much less reactive. This observation is important when an aryl halide or a vinyl halide is used to generate an aryllithium (such as 4-lithiotoluene)²⁵⁹ or a vinyllithium reagent.^{260,258} Heteroaryllithium reagents such as 3-lithiothiophene (**208**)²⁶¹ generated from 3-bromothiophene, are formed rapidly in ether solvents.^{255a} Coupling with alkyl halides is an important reaction of the relatively stable aryllithium reagents, as in the reaction of **208** with geranyl bromide (**209**) to give **210**.²⁶²



The disconnection for aryl alkylation is

$$R-CH_2R \longrightarrow R-CH_2X + R-X$$
 where R - alkyl or aryl

The lithium-halogen exchange is particularly useful for the preparation of stereodefined alkenyllithium reagents.²⁶³ Two equivalents of an organolithium reagent are necessary. When



Two equivalents of an organolithium reagent are necessary. When *n*-butyllithium reacts with **211**, one equivalent of *n*-butyllithium exchanges to form **212** plus 1-bromobutane and the second equivalent of *n*-butyllithium reacts with 1-bromobutane to form butene and butane. In this particular example,²⁶⁴ the geometric

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- 259. Gilman, H.; Langham, W.; Moore, F.W. J. Am. Chem. Soc. 1940, 62, 2327.
- 260. Merrill, R.E.; Negishi, E. J. Org. Chem. 1974, 39, 3452.
- 261. Moses, P.; Gronowitz, S. Arkiv. Kemi 1962, 18, 119 [Chem. Abstr. 56: 10173c 1962].
- 262. Semenovskii, V.V.; Emel'yanov, M. Izvest. Akad. Nauk. SSSR, Ser. Khim. 1980, 2578 (Engl., p 1833).
- 263. (a) Negishi, E. Organometallics In Organic Synthesis Vol. 1, Wiley-Interscience, New York, 1980, pp 39-40; (b) Kluge, H.F.; Untch, K.G.; Fried, J.H. J. Am. Chem. Soc. 1972, 94, 7827; (c) Cahiez, G.; Bernard, D.; Normant, J.F. Synthesis 1976, 245.
- 264. (a) Curtin, D.Y.; Crump, J.W. J. Am. Chem. Soc. 1958, 80, 1922; (b) Bordwell, F.G.; Landis, P.S. Ibid. 1957, 79, 1593; (c) Seyferth, D.; Vaughn, L.R. J. Organomet. Chem. 1963, 1, 201.

configuration of the 2-bromo-2-butenes **211** and **213** is retained upon metal-halogen exchange, giving the corresponding lithiobutenes (**212** and **214**, respectively). There is less isomerization of the alkenyl group during Li–H exchange than is observed with formation of the analogous Grignard reagent with magnesium. Stereodefined organolithium reagents are important for coupling reactions with alkyl halides. **Wurtz coupling** (*vide infra*, sec. 8.5.B.ii) is minimized when aryllithium or vinyllithium reagents are formed by metal-halogen exchange. An example is the reaction of vinyl bromide **213** with lithium, and subsequent reaction with iodooctane to give a 77% yield of **215** (94% *Z*).²⁶⁵ Alkenyllithium reagents react with aldehydes and ketones in the usual manner. Vinyllithium reagents, as well as other Grignard and organolithium reagents react with DMF to produce conjugated aldehydes. In Kende and co-worker's synthesis of *Stachybotrys* spirolactams,²⁶⁶ vinyl iodide **216** was treated with *tert*-butyllithium to initiate I \leftrightarrow Li exchange, and the resulting vinyllithium reagent reacted with an excess of DMF to give a 83% yield of conjugated aldehyde **217**.



The alkenyllithium-alkyl halide disconnection is:

$$\underset{R}{\overset{OH}{\longrightarrow}} \underset{R^{1}}{\overset{R^{1}}{\longrightarrow}} \underset{R^{-CHO}}{\overset{R}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{O}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{O}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{O}{\longrightarrow}} \underset{R}{\overset{O}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{O}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{O}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{R}{\longrightarrow}} \underset{R}{\overset{R}{\overset}} \underset{R}{\overset}} \underset{R}{\overset{R}{\overset}} \underset{R}{\overset}} \underset{R}{\overset}} \underset{$$

8.5.B.ii. Wurtz Coupling. There are two major side reactions in a metal-halogen exchange reaction between an organolithium reagent and an alkyl halide, coupling (the Wurtz reaction, 267,268 which generates R–R, R¹–R¹, and R–R¹) and α -metalation. The halogen is

 ⁽a) Stowell, J.C. Carbanions in Organic Synthesis Wiley Interscience, New York, 1979, p 50; (b) Millon, J.; Lorne, R.; Linstrumelle, G. Synthesis 1975, 434; (c) Cahiez, G.; Masuda, A.; Bernard, D.; Normant, J.F. Tetrahedron Lett. 1976, 3155; (d) Cahiez, G.; Bernard, D.; Normant, J.F. Synthesis 1977, 130; (e) Cahiez, F. Normant, J.F. Tetrahedron Lett. 1977, 3383.

^{266.} Deng, W.-P.; Zhong, M.; Guo, X.-C.; Kende, A.S. J. Org. Chem. 2003, 68, 7422.

^{267. (}a) Wurtz, A. Ann. Chim. Phys. 1855, 44, 275; (b) Idem Annalen 1855, 96, 364.

^{268. (}a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-104; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 708-709.

electron withdrawing, making the proton on the α -carbon acidic, which facilitates its removal by the basic organometallic. As noted for the **Kharasch reaction** with Grignard reagents (sec. 8.4.B.i), this sort of exchange leads to two organolithium reagents and two halides, with direct coupling products R–R and R¹–R¹ as well as a cross coupling product R–R¹. Wurtz coupling also occurs during metal-halogen exchange reactions, forming R–R.

$$\begin{array}{rcl} R-Li + R^{1}-X & \longrightarrow & R-R + R^{1}-R^{1} + R-R^{1} \\ M + R-X & \longrightarrow & R-R + M-X + R-M \end{array}$$

Wurtz coupling can be avoided by using an organotin compound as a precursor to the organolithium reagent.²⁶⁹ Allyllithium (**219**) is often difficult to prepare by the usual metal-halogen exchange methods. An alternative synthesis first reacted allyl bromide with triphenyltin hydride (Ph₃SnH) to give allyltriphenyltin (**218**). Subsequent metal-metal (Sn–Li) exchange with phenyllithium gave an excellent yield of **219** along with tetraphenyltin (Ph₄Sn).²⁶⁷ This route is useful when the organolithium reagent is very reactive, or when the halide does not undergo exchange at a reasonable rate (as with vinyl bromide to give vinyllithium).²⁷⁰

$$Br \xrightarrow{Ph_3SnH} SnPh_3 \xrightarrow{PhLi} Li + Ph_4Sn$$

Reactive halides, such as allyl or benzyl halides, usually give Wurtz coupling during lithiumhalogen exchange, leading to low concentrations of the organolithium reagent. Less reactive alkyl halides often fail to react at all. Addition of cuprous salts greatly enhances the reaction with alkyl halides, but this generates a new reagent, a lithium dialkylcuprate. This important class of reagents will be discussed in Section 8.7.A.

8.5.C. Reactions with Aldehydes and Ketones

The reactions of organolithium reagents (RLi) parallel those of Grignard reagents (RMgX) in many ways.¹⁰³ Williard and co-worker's *ab initio* study of the reaction of methyllithium aggregates with formaldehyde in aqueous media showed one formaldehyde and one water around lithium ions, coordinating the reactive methyl group via polar solvation.²⁷¹ Addition occurred via a concerted mechanism involving a four-membered ring transition state, but hydrophobic solvents and low substrate concentrations promoted a non-concerted mechanism involving ring opening of the dimers and the trimer. Organolithium reagents that are not commercially available can be prepared, such as the organolithium reagent derived from **216**. Commercially available organolithium reagents can be added to carbonyl derivatives, and often provide the most efficient route to substituted alcohols. Organolithium reagents react

^{269.} Gröbel, B.-T.; Seebach, D. Chem. Ber. 1977, 110, 867.

 ⁽a) West, R.; Glazer, W.H. J. Org. Chem. 1961, 26, 2096; (b) Seyferth, D.; Weiner, M.A. Chem. Ind. (London) 1959, 402; (c) Juenge, E.C.; Seyferth, D. J. Org. Chem. 1961, 26, 563.

^{271.} Hæffner, F.; Sun, C.; Williard, P.G. J. Am. Chem. Soc. 2000, 122, 12542.

with ketones and aldehyde via acyl addition, as expected of a carbon nucleophile. In a synthesis of briarellin E,²⁷² Overman and co-worker's converted vinyl iodide **220** to the corresponding vinyl iodide, and subsequent reaction with aldehyde **221** gave **222** as a 3:1 mixture of *anti:syn* diastereomers, in 62% yield.



Unlike similar reactions with Grignard reagents, reduction is not a serious problem.²⁷³ *n*-Butyllithium, for example, added readily to the hindered ketone di-*tert*-butyl ketone (**223**) to give alcohol **224** by direct addition to the carbonyl.^{273b} Organolithium reagents usually prefer 1,2-addition in conjugated systems due primarily to their enhanced nucleophilicity and poor coordinating ability relative to Grignard reagents. The reaction of methyllithium with **225**, for example, gave an 88% yield of **226** in Sha and co-worker's synthesis of (–)-pinguisenol.²⁷⁴ Although the C=C unit in **225** is sterically hindered, 1,2-addition is the normal reaction. Indeed, reaction of methyllithium with 3-penten-2-one gave < 1% of conjugate addition, with 2-methyl-3-penten-2-ol being the major product.²⁷⁵ Note that addition of cuprous iodide to the reaction led to > 99% of conjugate addition²⁷⁵ (sec. 8.7.A.vi).



The disconnection for organolithium addition is



8.5.D. STEREOSELECTIVITY IN ORGANOLITHIUM REACTIONS

8.5.D.i. Configurational Stability. As with Grignard reagents, it is important to know if an organolithium reagent with a stereogenic carbon at the C–Li unit is configurationally

^{272.} Corminboeuf, O.; Overman, L.E.; Pennington, L.D. J. Am. Chem. Soc. 2003, 125, 6650.

^{273. (}a) Huet, F.; Emptoz, G. J. Organomet. Chem. 1975, 101, 139; (b) Buhler, J.D. J. Org. Chem. 1973, 38, 904.

^{274.} Sha, C.-K.; Liao, H.-W.; Cheng, P.-C.; Yen, S.-C. J. Org. Chem. 2003, 68, 8704.

^{275. (}a) House, H.O.; Respess, W.L.; Whitesides, G.M. J. Org. Chem. 1966, 31, 3128; (b) Braude, E.A.; Timmons, C.J. J. Chem. Soc. 1950, 2007; (c) Gilman, H.; Kirby, R.H. J. Am. Chem. Soc. 1941, 63, 2046.

stable in subsequent reactions. In general, such stereogenic centers are not very stable and undergo racemization²⁷⁶ unless cyclopropyl halides are used as precursors, similar to the diastereoselectivity noted with cyclopropyl Grignard reagents (sec. 8.4.F.i). Reaction of halide **227** (X = Cl, Br, I) with lithium metal, followed by quenching with CO₂, gave carboxylic acid **228**.¹⁶³ The amount of racemization varied as the halide was changed. Table 8.12¹⁶³ shows the % of racemization observed when the organolithium reagent is generated from R-X. It follows the order: I > Br > Cl, where R is a cyclopropyl group. Reaction of **227** [X = I, 1% sodium (25 microns)] gave 64% racemization, but decreasing the sodium concentration to 0.002% gave 87% racemization. An increase in the particle size of the sodium increased the amount of racemization. Both results are consistent with a complex heterogeneous surface reaction. The nature of the halide, the percentage of Na, and the particle size all contribute to the relative rate of formation of the organolithium as well as the stereoselectivity of the reaction.²⁷⁷ Note that the choice of solvent can also influence the stereochemistry of organolithium reactions. There is some evidence that organolithium reagents have greater stereochemical stability in hydrocarbon solvents than they do in ether.²⁷⁸

	227 Ph	$Me = \frac{1. L}{2. C}$ $X = \frac{3. H}{3. H}$	$\stackrel{i^{o}, \text{ ether}}{\overset{O_{2}}{_{3}O^{+}}}$ $\stackrel{Me}{\overset{CO_{2}}{_{2}}}$	н 228
X	Time (min)	<u>% 228</u>	<u>Optical Purity (%)</u>	Racemization (%)
Cl	40	73	71	29
Cl	60	76	66	34
Br	32	60	46	54
Br	42	70	42	58
Ι	33	42	36	64
Ι	41	60	36	64
[Reprinted with permission from Walborsky, H.M.; Impastato, F.J.; Young, A.E. J. Am. Chem. Soc. 1964, 86, 3283. Copyright © 1964 American Chemical Society.]				

Table 8.12. Racemization of Cyclopropyllithium with Changes in Halide

8.5.D.ii. Diastereoselective Addition Reactions. If the ketone or aldehyde contains a stereogenic center α - to the carbonyl, addition of the organolithium reagent can give a product with good diastereoselectivity. The stereoselectivity of addition for Grignard reagents and organolithium reagents with aldehydes and ketones is predicted in a manner similar to that observed with reducing agents in section 4.8. Acyl addition of organolithium reagents to ketones and aldehydes usually follows Cram's rule (sec. 4.8.B), for example, as seen in Table

⁽a) Witanowski, M.; Roberts, J.D. J. Am. Chem. Soc. 1966, 88, 737; (b) Lardicci, L.; Lucarini, L.; Palagi, P.; Pino, P. J. Organomet. Chem. 1965, 4, 341; (c) Buncel, E. Carbanions: Mechanistic and Isotopic Aspects, Elsevier, 1975.

^{277.} Walborsky, H.M.; Aronoff, M.S. J. Organomet. Chem. 1965, 4, 418.

^{278. (}a) Curtin, D.Y.; Koehl, Jr., W.J. J. Am. Chem. Soc. 1962, 84, 1967; (b) Reference 216, pp 697-698.

8.13.²⁷⁹ Since lithium does not coordinate as readily as magnesium in reactions with carbonyls, chelation effects are somewhat diminished relative to Grignard reagents, and the Cram cyclic model is not as useful for predicting the selectivity. When complexing agents are added to the reaction, however, the cyclic model does predict the major diastereomer. Table 8.13, taken from Mosher and Morrison's work, shows the usual Cram selectivity for ketone **229** with a variety of organolithium reagents. The products are diastereomeric alcohols **230** and **231**.

	R _M , R _S R _L 229	$R^1 \xrightarrow{1. R^2 Li} 2. H_2O$	HO R _M R _S R _L 23 ($\begin{array}{c} R^2 \\ R^1 \\ \end{array} + \begin{array}{c} R_M \\ R_S \\ R_L \\ \end{array}$	€ ^{OH} _{R¹} 31
<u>R</u> s	<u>R</u> M	$\underline{\mathbf{R}}_{\mathbf{L}}$	$\underline{\mathbf{R}}^{1}$	$\underline{\mathbf{R}}^2$	<u>230 : 231</u>
Н	<i>i</i> -Pr	Ph	Н	<i>i</i> -Pr	1:1
Me	Et	Ph	Me	Et	2.3:1
Me	Et	Ph	Et	Me	10:1
Н	Me	cyclohexyl	Н	Me (in pentane)	1.5 : 1
Н	Me	cyclohexyl	Н	Me (in ether)	1.2 : 1
[Reprinted by Asymmetric	[Reprinted by courtesy of Professor James D. Morrison from Morrison, J.D.; Mosher, H.S. <i>Asymmetric Organic Reactions</i> , American Chemical Society, Washington, D., 1976, pp. 92-93.]				

 Table 8.13. Cram Selectivity in Reactions of Organolithium Reagents with Ketones and Aldehydes

Reaction with cyclic ketones usually favors formation of the syn diastereomer as shown in Table 8.14.²⁸⁰ As with Grignard reagents, attack at a carbonyl occurs at the less sterically hindered face of the molecule. Reaction of various organolithium and Grignard reagents with 2-methylcyclopentanone, for example, gave a mixture of cis- (232) and trans- (233) alcohols, generally favoring 232.

Table 8.14.Selectivity in Reactions of 2-Methylcyclopentanone with Organolithium
Reagents and Grignard Reagents

Me Ne	R—M	OH Me + 232 +	R Me 233
<u>RM</u>	<u>Solvent</u>	<u>232 : 233</u>	<u>% Yield</u>
MeLi	ether	70:30	53
MeMgI	ether	45 : 55	95
EtMgBr	THF	75 : 25	68
n-PrMgBr	ether	80:20	50
C ₆ H ₁₃ MgBr	ether	80:20	53
PhLi	ether	95 : 5	53
PhMgBr	THF	99:1	60

^{279.} Reference 162, pp 92-93.

^{280.} Battioni, J.-P.; Capmau, M.-L.; Chodkiewicz, W. Bull. Soc. Chim. Fr. 1969, 976.

8.5.E. Reactions of Organolithium Reagents with Other Functional Groups

Organolithium reagents react with carbonyl compounds other than aldehydes and ketones analogous to Grignard reagents.¹⁰⁷ Esters usually react to give a tertiary alcohol,²⁸¹ and acid chlorides²⁸² give mixtures of unreacted starting material and tertiary alcohol. Adding an excess of the organolithium reagent gives the tertiary alcohol exclusively, which is formally analogous to the acyl substitution reactions noted for Grignard reagents (sec. 8.4.C.ii). If an ester is treated with excess methyllithium, a tertiary dimethyl carbinol results as in the conversion of **234** to **235** (95%) in Venkateswaran and co-worker's synthesis of heliannuol B.²⁸³ Careful selection of RLi and the reaction conditions often allows the synthesis of ketones rather than tertiary alcohols, however.²⁸⁴



Reaction with amides can give a ketone,^{123,285} but removal of the proton on the α -carbon of amides or lactams by the basic organolithium to form an enolate anion is a common side reaction. For this reason, non-nucleophilic bases such as lithium diisopropylamide are commonly used (sec. 9.2.B).²⁸⁶ Organolithium reagents react with Weinreb's amide (see sec. 2.5.C) to give ketones, just as it was noted for Grignard reagents in Section 8.4.C.ii.²⁸⁷ Primary amides react with excess organolithium to give a nitrile, as in the conversion of phenylacetamide (**236**) to benzonitrile in 72% yield.²⁸⁸ Reaction of **236** with three equivalents of butyllithium gave trilithiated species **237**, fragmentation gave **238** and hydrolysis gave benzonitrile.²⁸⁸

^{281. (}a) Nelson, P.H.; Strosberg, A.M.; Untch, K.G. J. Med. Chem. 1980, 23, 180; (b) Kleemann, A.; Hesse, J.; Engel, J. Arzneim-Forsch. 1981, 31, 1178 [Chem. Abstr. 95: 186978q 1981].

^{282.} Locksley, H.D.; Murray, I.G. J. Chem. Soc. C 1970, 392.

^{283.} Roy, A.; Biswas, B.; Sen, P.K.; Venkateswaran, R.V. Tetahedron Lett. 2007, 48, 6933.

^{284. (}a) Corey, E.J.; Kim, S.; Yoo, S.-e.; Nicolaou, K.C.; Melvin, Jr., L.S.; Brunelle, D.J.; Falck, J.R.; Trybulski, E.J.; Lett, R.; Sheldrake, P.W. *J. Am. Chem. Soc.* **1978**, 100, 4620; (b) Corey, E.J.; Trybulski, E.J.; Melvin, Jr., L.S.; Nicolaou, K.C.; Secrist, J.A.; Lett. R.; Sheldrake, P.W.; Falck, J.R.; Brunelle, D.J.; Haslanger, M.F.; Kim, S.; Yoo, S.-e. *Ibid.* **1978**, 100, 4618; (c) Corey, E.J.; Melvin, Jr., L.S.; Haslanger, M.F. *Tetrahedron Lett.* **1975**, 3117.

^{285. (}a) Evans, E.A. J. Chem. Soc. 1956, 4691; (b) Jones, E.; Moodie, I.M. J. Chem. Soc. C, 1968, 1195.

^{286. (}a) Hullot, P.; Cuvigny, T.; Larchevêque, M.; Normant, H. Can. J. Chem. 1976, 54, 1098; (b) Durst, T.; Van Den Elzen, R.; Legault, R. Ibid. 1974, 52, 3206; (c) Crouse, D.N.; Seebach, D. Berichte 1968, 101, 3113.

For a synthetic example taken from a synthesis of (+)-frontalin, see Kanada, R.M.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* 2000, 41, 3631.

^{288.} Kaiser, E.M.; Vaulx, R.L.; Hauser, C.R. J. Org. Chem. 1967, 32, 3640.

$$\begin{array}{c} Ph \longrightarrow NH_2 & 3 \text{ } n\text{-}C_4H_9Li \\ O & THF-hexane \end{array} \begin{bmatrix} Li \\ Ph & N\text{-}Li \\ OLi \end{bmatrix} \longrightarrow \begin{bmatrix} Li \\ Ph & C=N \end{bmatrix} \xrightarrow{H_3O^+} Ph & C=N \\ \begin{array}{c} 236 & 237 & 238 \end{array}$$

In section 8.5.B.i the reaction of a Grignard reagent with DMF (an amide) gave an aldehyde, and organolithium reagents react similarly. An example is taken the synthesis of geldanamycin by Andrus and co-workers,²⁸⁹ in which the reaction of **239** with *n*-butyllithium gave an aryllithium reagent (see sec. 8.5.F for directed ortho metalation reactions), which reacted with DMF *in situ* to give aryl aldehyde **240** in 79% yield after hydrolysis.

Organolithium addition to acid derivatives gives the disconnections:

$$\begin{array}{c} OH \\ R + R^1 \\ R^1 \end{array} \xrightarrow{R - CO_2 X} + R^1 - X \\ R + R^1 \\ R^1 \end{array} \xrightarrow{O} R - CO_2 X + R^1 - X \\ R + R^1 \\ R^1 \end{array}$$

Organolithium reagents are more reactive than the corresponding Grignard reagent. A comparison with Grignard reagents readily demonstrates this statement. The reaction of a Grignard reagent and a carboxylic acid gives the carboxylate salt. Reaction of an organolithium reagent with a carboxylic acid gives the expected lithium carboxylate salt, but a second equivalent adds to the carboxylate to give a ketone. 2-Furyllithium (241) reacted with acetic acid, for example, to give the dianion (242).²⁹⁰ Hydrolysis of 242 gave the hydrate, which was converted to the ketone (243) under the reaction conditions. The reaction of 242 with acetic acid *in situ*, however generated some ketone product prior to the hydrolysis step. In the presence of an excess of the furyllithium reagent, further reaction gave alcohol 244 as a byproduct.²⁹⁰



The disconnection for ketone formation from the acid is:

$$R^{O}$$
 $R^{-CO_2H} + R^1 - X$

^{289.} Andrus, M.B.; Hicken, E.J.; Meredith, E.L.; Simmons, B.L.; Cannon, J.F. Org. Lett. 2003, 5, 3859.

^{290.} Heathcock, C.H.; Gulik, L.G.; Dehlinger, T. J. Heterocyclic Chem. 1969, 6, 141.

Organolithium reagents react vigorously with carbon dioxide to give the corresponding carboxylic acid after hydrolysis. Typically, the organolithium solution is carefully poured onto dry ice. An example is taken from Maier and Kühnert's synthesis of apicularen A,²⁹¹ in which carboxylic acid **246** was prepared from **245** in 77% yield. We saw this reaction earlier when cyclopropyllithium reagent **227** was quenched with CO₂.



Nitriles can be hydrolyzed to or prepared from carboxylic acids, and nucleophiles²⁹² can attack the electrophilic carbon, so they are considered to be acid derivatives. 3-Thienyllithium (**208**) reacted with 4-methylpyridine carbonitrile (**247**), for example, to give a *N*-lithio imine (**248**) analogous to the reaction of Grignard reagents. Subsequent acid hydrolysis converted the initially formed imine to the ketone **249**.²⁹³ Addition of an organolithium reagent initially generates an imine, so reduction to an amine (secs. 4.2.C.iii, 4.4.A, 4.5.A) is also possible. Reaction of butyllithium with nitrile **250**, for example, gave an 84% yield of lithiated imine **251**.²⁹⁴ and reduction with methanolic sodium borohydride gave a 90% yield of amine **252**.



The disconnections for these two reactions are:

- 291. Kühnert, S.M.; Maier, M.E. Org. Lett. 2002, 4, 643.
- 292. (a) Reference 219, p 698; (b) O'Sullivan, W.I.; Swamer, F.W.; Humphlett, W.J.; Hauser, C.R. *J. Org. Chem.* **1961**, *26*, 2306.
- 293. (a) Granados Jarque, R.; Bosch Cartes, J.; Lopez Calahorra, F. Spanish Patent 453,484 [Chem. Abstr. 90: P152156b 1979]; (c) Koshinaka, E.; Ogawa, N.; Yamagishi, K.; Kato, H.; Hanaoka, M. Yakugaku Zasshi 1980, 100, 88 [Chem. Abstr. 93: 71507b 1980].
- 294. (a) Zhu, J.; Quirion, J.-C.; Husson, H.-P. *Tetrahedron Lett.* **1989**, *30*, 6323; (b) Arseniyadis, S.; Huang, P.Q.; Husson, H.-P. *Ibid.* **1988**, *29*, *1391*.

8.5.F. Directed Ortho Metalation

When an aromatic ring has a heteroatom or a heteroatom-containing substituent, reaction with a strong base such as an organolithium reagent usually leads to an ortho lithiated species.²⁹⁵ Subsequent reaction with an electrophilic species gives the ortho substituted product. Gilman and by Wittig discovered this ortho selectivity independently in 1939-1940, when anisole was found to give ortho deprotonation in the presence of butyllithium.²⁹⁶ This reaction generated ortho-lithiated anisole (253), and subsequent reaction with CO₂ gave 2-methoxybenzoic acid (254).^{296a} Hauser and co-workers greatly contributed to this reaction.²⁹⁷ Snieckus²⁹⁸ provides a table of relative directing abilities of various groups, and several categories of functional groups are capable of this ortho-directing effect. When two directing metalation groups have a 1,3-relationship on the aromatic ring, they work cooperatively to enhance the ortho selectivity.²⁹⁹ An example is taken from Moriarty and coworker's synthesis of treprostinil.³⁰⁰ Treatment of anisole derivative 255 with butyllithium and then allyl bromide, gave a 60% yield of 256. Collum and co-worker's rate studies of the butyllithium-TMEDA mediated lithiation reaction of five arenes suggest that the lithiation reactions do not necessarily rely on a complexinduced proximity effect.³⁰¹ They³⁰¹ proposed a triple-ion based model that depends largely on inductive effects proposed by Schlosser.302



- 295. For a review of directed ortho metalation, see (a) Snieckus, V. Chem. Rev. 1990, 90, 879; (b) Gschwend, H.W.; Rodriguez, H.R. Org. React. 1979, 26, 1. Also see (c) Green, L.; Chauder, B.; Snieckus, V. J. Heterocyclic Chem. 1999, 36, 1453.
- 296. (a) Gilman, H.; Bebb, R.L. J. Am. Chem. Soc. 1939, 61, 109; (b) Wittig, G.; Fuhrman, G. Chem. Ber. 1940, 73, 1197.
- 297. (a) Puterbaugh, W.H.; Hauser, C.R. J. Org. Chem. 1964, 29, 853; (b) Slocum, D.W.; Sugarman, D.I. Adv. Chem. Ser., 1974, No. 130, 227.
- 298. See reference 295a, and Scheme 7 therein (pp. 884-885).
- 299. See reference 295a, and Table 3 therein (p 885) for cooperative effects of several 1,3-related directed metalation groups.
- 300. Moriarty, R.M.; Rani, N.; Enache, L.A.; Rao, M.S.; Batra, H.; Guo, L.; Penmasta, R.A.; Staszewski, J.P.; Tuladhar, S.M.; Prakash, O.; Crich, D.; Hirtopeanu, A.; Gilardi, R. J. Org. Chem. 2004, 69, 1890.
- 301. (a) Chadwick, S.T.; Rennels, R.A.; Rutherford, J.L.; Collum, D.B. J. Am. Chem. Soc. 2000, 122, 8640. Also see (b) Collum, D.B. Acc. Chem. Res. 1992, 25, 448
- 302. (a) Maggi, R.; Schlosser, M. *Tetrahedron Lett.* 1999, 40, 8797; (b) Schlosser, M. Angew. Chem. Int. Ed. 1998, 37, 1497; (c) Büker, H.H.; Nibbering, N.M.M.; Espinosa, D.; Mongin, F.; Schlosser, M. *Tetrahedron Lett.* 1997, 38, 8519.

As a rule, the powerful organolithium bases should be used with organic solvents in which they are highly soluble, due to their association into aggregates (see sec. 8.5.A).^{295a} Additives such as TMEDA are usually important because they effectively break down the aggregates (see sec. 8.5.A) to generate monomers and dimers in solution.³⁰¹ Roberts and Curtin proposed that ortho lithiated species are stabilized by coordination many years ago,³⁰³ and Snieckus summarized the early evidence pointing to the idea that the directed ortho-lithiation process is a three-step sequence.^{295a} The three steps are coordination to give the coordinated ortho-lithiated species, and finally, reaction with an electrophile to give the final product as with any organolithium reagent.

As mentioned, many groups are capable of directed ortho metalation, which is illustrated by the reaction of *N*-cumylbenzamide (**257**) with 3.2 equivalents of *sec*-butyllithium in the presence of TMEDA to give **258**³⁰⁴ as a reactive intermediate. Subsequent treatment with benzaldehyde gave an 86% yield of **259**. The reaction is not limited to simple aromatic rings. In a synthesis of (+)-aigialospirol by Hsung and co-worker's, aryl amide **260** was treated with an excess of *sec*-butyllithium and then with an excess of TMEDA to give the *ortho*-lithiated amide **261**.³⁰⁵ Subsequent treatment with aldehyde **262** gave **263** in 50% overall yield. In previous examples, the conversion of **239** to **240** and **245** to **246** exploited this chemistry. This regioselective approach to preparing functionalized aromatic rings is an important addition to synthetic methodology.



A disconnection for these reactions is generalized as:



^{303. (}a) Roberts, J.D.; Curtin, D.Y. J. Am. Chem. Soc. 1946, 68, 1658; (b) Morton, A.A. J. Am. Chem. Soc. 1947, 69, 969; (c) Chatgilialoglu, C.; Snieckus, V. in Chemical Synthesis Gnosis to Prognosis; NATO ASI Series E. Applied Sciences, Vol. 320, p 191. Kluwer Academic Publishers, Netherlands, 1994.

^{304.} Chauder, B.; Green, L.; Snieckus, V. Pure Appl. Chem. 1999, 71, 1521.

^{305.} Figueroa, R.; Hsung, R.P.; Guevarra, C.C. Org. Lett., 2007, 9, 4857.

8.5.G. Addition to Epoxides, Alkenes, and Alkynes

8.5.G.i. Reactions with Epoxides. Epoxides are opened to the alcohol as expected, untroubled by the MgX₂ catalyzed rearrangements often observed with Grignard reactions. Methyllithium reacted with epoxide **264** to give the alcohol (**265**), in 68% yield.³⁰⁶ The methyllithium added selectively to the allylic position to give the (*E*)-carbinol. In general, the organolithium attacks the epoxide at the less sterically hindered (less substituted) carbon, as was noted with Grignard reagents (8.4.E.).



The epoxide ring opening gives the disconnection:



8.5.G.ii. Intramolecular Addition to Alkenes and Alkynes. While organolithium reagents react with alkenes or alkynes in an intramolecular reaction, both are relatively inert to the analogous intermolecular reaction. Ward and Lawler treated alkynyl bromide **266** with *n*-butyllithium, which gave a 60% yield of the alkylidene cyclopentane **267**.³⁰⁷ There were several other products produced in this reaction, and the mechanistic pathway for the cyclization was not well understood. Bailey et al. showed that the *tert*-butyllithium exchange reaction and the cyclization reaction are rapid at low temperatures. Reaction of 6-iodo-3-methyl-1-hexene (**268**) gave **269**, which cyclized to a mixture of **270** and **271**. Quenching with methanol at -78°C gave a mixture of 76% of **273**, 5.6% of **274** and 14.2% of uncyclized product **272**.³⁰⁸



^{306.} Edward, D.E.; Ho, P.T. Can. J. Chem. 1977, 55, 371.

^{307.} Ward, H.R.; Lawler, R.G. J. Am. Chem. Soc. 1967, 89, 5517.

^{308.} Bailey, W.F.; Nurmi, T.T.; Patricia, J.J.; Wang, W. J. Am. Chem. Soc. 1987, 109, 2442.

Bailey et al. also showed the initially formed organolithium product could be trapped with a variety of electrophiles, including aldehydes.³⁰⁹ Cooke has shown that alkyllithium and alkenyllithium derivatives containing an ester moiety can be cyclized to form ketone products by direct addition or by Michael addition.³¹⁰ Bicyclic and spirocyclic molecules can be prepared by addition of TMEDA to the initially formed organolithium, because it induces a second cyclization reaction. The organolithium products were trapped with various electrophiles.³¹¹ There is good enantioselectivity in the presence of (–)-sparteine. The reaction of **275** with *tert*-butyllithium and (–)-sparteine (**163**) gave **276**, which cyclized to give **277**. Quenching with water gave **278** in 60% yield (65% ee), in ether, and 85% yield (87% ee) in toluene.³¹² When the reaction was done in THF, however, an 80% yield of **278** was obtained but with 0% ee. The extent of asymmetric induction is dependent on the structure of the added ligand.³¹³



8.5.H. Basicity: Metal-Hydrogen Exchange

Organolithium reagents are stronger bases than Grignard reagents so removal of the acidic α -hydrogen to form an enolate anion can be a problem in reactions with carbonyl derivatives. Addition to the carbonyl of ketones and aldehydes is the faster process with common organolithium reagents. Specialized organolithium reagents can give different results, however. Lithium triphenylmethide, for example, often gives selective deprotonation with aldehydes and ketones. The extent of enolate formation with organolithium is dependent on many factors.³¹⁴ Because organolithium reagents are powerful bases,³¹⁵ the metal-hydrogen exchange reaction with functionalized substrates plays an important role in many syntheses.³¹⁶ This exchange reaction is believed to proceed via a four-center transition state such as **279**, generating a new organolithium (R–Li) from the acid (R–H + R¹–Li).^{220,317} For this reaction to occur, R–H

- 313. Mealy, M.J.; Luderer, M.R.; Bailey, W.F.; Sommer, M.B. J. Org. Chem. 2004, 69, 6042.
- 314. House, H.O.; Kramar, V. J. Org. Chem. 1963, 28, 3362.
- 315. Roberts, J.D.; Curtin, D.Y. J. Am. Chem. Soc. 1946, 68, 1658.
- 316. (a) Reference 219, pp 698-705; (b) Reference 218.

^{309.} Bailey, W.F.; Ovaska, T.V.; Leipert, T.K. Tetrahedron Lett. 1989, 30, 3901.

⁽a) Cooke, Jr., M.P. J. Org. Chem. 1992, 57, 1495; (b) Cooke, Jr., M.P.; Widener, R.K. Ibid. 1987, 52, 1381;
(c) Cooke, Jr., M.P. Ibid. 1984, 49, 1144; (d) Cooke, Jr., M.P.; Houpis, I.N. Tetrahedron Lett. 1985, 26, 4987.

^{311.} Bailey, W.F.; Khanolkar, A.D. J. Org. Chem. 1990, 55, 6058.

^{312. (}a) Gil, G.S.; Groth, U.M. J. Am. Chem. Soc. 2000, 122, 6789. For the identical reaction with the N,Ndiallyl derivative, see (b) Bailey, W.F.; Mealy, M.J. J. Am. Chem. Soc. 2000, 122, 6787.

^{317. (}a) Ingold, C.K. Helv. Chim. Acta 1964, 47, 1191; (b) Batalov, A.P.; Rostokin, G.A.; Korshunov, I.A. J. Gen. Chem. USSR 1965, 35, 2146 (Engl., p 2135).

must be a stronger acid than R^1 –H, and R^1 –Li must be a stronger base than R–Li. The ratedetermining step³¹⁸ in cleavage of the C–H bond is initial coordination of the lithium atom with the atom bearing the most acidic hydrogen,^{287,319} In general, the more acidic the proton being removed in R–H, the more facile the reaction with R¹–Li. Six factors influence the acidity of a C–H bond.³²⁰

$$R-H + R^{1}-Li \longrightarrow \begin{bmatrix} R-H & R-H & R-H \\ \vdots & \vdots & \vdots \\ Li \cdot R^{1} & 279 \end{bmatrix} \xrightarrow{R-Li + R^{1}-H}$$

Table 8.15. The pK_a as a Function of % s Character

Compound	Bond Hybridization	<u>% s-Character</u>	pK _a
ethyne	sp	50	25
ethene	sp^2	33	36.5
cyclopropane	sp ^{2.28}	30	39
ethane	sp ³	25	42

- 1. The first factor is the percentage of s character.^{320a} As the s character of a bond increases, the attached proton becomes more acidic, because the 2s orbital lies closer to the nucleus than the 2p orbitals. When the proton is removed, increased electron density in the 2s orbital gives greater stability to the carbanion. As shown in Table 8.15,^{320a} this leads to enhanced acidity of the alkynyl C–H relative to the analogous alkenyl C–H. Diminishing the C–C–C bond angle (i.e., cyclopropane) increases the % s character, and a cyclopropane C–H is more acidic than a normal alkane hydrogen. The percentage of s character³²¹ can be determined from ¹³C NMR nuclear spin-spin coupling constants.
- 2. Conjugative effects enhance the acidity of certain covalently bound hydrogen atoms.^{320a} The presence of a substituent that can delocalize electron density toward a more electronegative atom makes that proton more acidic. In addition, the conjugate base (the carbanion) formed after its removal is more stable because the electrons can be delocalized over several atoms. Carbonyl groups provide delocalization in the resonance stabilized enolate anion 280, for example. The alkene bond linkage in enolate anion 280 is usually planar, but steric interactions, reduction of bond angles in small rings, and solvent interactions can inhibit formation of the planar enolate. The

 ⁽a) Shatenshtein, A.I.; Kamrad, A.G.; Shapiro, I.O.; Ranneva, Yu.I.; Zvyagintseva, E.N. Dokl. Akad. Nauk, SSSR 1966, 168, 364; (b) Barnes, R.A.; Nehmsmann, L.J. J. Org. Chem. 1962, 27, 1939; (c) Benkeser, R.A.; Trevillyan, A.E.; Hooz, J. J. Am. Chem. Soc. 1962, 84, 4971; (d) Bryce-Smith, D. J. Chem. Soc. 1963, 5983.

^{319. (}a) Morton, A.A. J. Am. Chem. Soc. 1947, 69, 969; (b) Gilman, H.; Morton, Jr., J.W. Org. React. 1954, 8, 258.

^{320. (}a) Reference 49a, pp 48-85; (b) Bent, H.A. Chem. Rev. 1961, 61, 275; (c) Walsh, A.D., Trans. Faraday Soc. 1949, 45, 179.

^{321.} Closs, G.L.; Closs, L.E. J. Am. Chem. Soc. 1963, 85, 2022.

stabilizing effects of conjugation are diminished in an enolate anion as a result of these factors³²² (sec. 9.2). The proton H_a in diketone **281**, for example, is much less acidic when compared to H_a in dione **282**.³²² This effect has been attributed to poor overlap of the carbanion orbital with the p orbitals of the carbonyl in **281**, due to the steric constraints of the bicyclo[2.2.2]octane ring system. The diminished acidity is therefore not entirely due to the difficulty that arises when forming a planar enolate. Aryl and alkenyl groups also provide conjugative stabilization, as in the benzyl anion (**283**). Conjugating groups such as nitro and cyano are excellent stabilizing substituents, as shown in **284** and **285**, respectively.



- **3.** Inductive effects^{320a} involve both through bond transmission of electrons, and field (through space) effects (sec. 2.2.A). As the electronegativity of a substituent increases, the central atom diverts increasing amounts of s character to the orbital occupied by the unshared electron pair.^{320a} Methoxyacetic acid (pK_a 3.57) is more acidic, for example, than acetic acid (pK_a 4.75).³²³ Most carbanion stabilizing groups act through a mixture of inductive and conjugative effects that are difficult to separate. The fluoride anion and quaternary ammonium cations are the only common substituents that stabilize ions by pure inductive effects.
- 4. Homoconjugative effects^{320a} occur when the α -carbon (the position adjacent to a group that induces acidity) is blocked, but the β -carbon bears a hydrogen. Removal of the β -hydrogen of certain ketones (called β -enolization) can give a stabilized carbanion, when its p orbital is held rigidly at the proper angle and distance to the p orbital of the carbonyl. The effect³²⁴ is usually limited to a compound where an acidic proton is disposed β to the carbonyl, and the α -position does not possess hydrogen atoms. A **homoenolate** (first reported by Nickon and co-workers) is believed to be resonance stabilized by species such as **287** and **288**,³²⁵ derived from treatment of **286** with base.³²⁶

^{322.} Bartlett, P.D.; Woods, G.F. J. Am. Chem. Soc. 1940, 62, 2933.

^{323.} King, E.J. J. Am. Chem. Soc. 1960, 82, 3575.

^{324.} Johnson, A.L.; Petersen, W.W.; Rampersad, M.B.; Stothers, J.B. Can. J. Chem. 1974, 52, 4143.

^{325.} Nickon, A.; Kwasnik, H.; Swartz, T.; Williams, R.O.; DiGiorgio, J.B. J. Am. Chem. Soc. 1965, 87, 1615.

^{326.} Werstiuk, N.H. Tetrahedron 1983, 39, 205.

The acidity of H_a in **286** is thereby enhanced.³²⁷



5. Aromatic character^{320a} is an important consideration when comparing the conjugate bases of several weak acids. If one of the conjugate bases is a resonance stabilized anion, the acid precursor will be more acidic when compared to an acid that generates a non-aromatic conjugate base. The pK_a of cyclopentadiene is ~ 15, due in part to removal of a proton that leads to the stable aromatic cyclopentadienyl anion **289**. This acidity sharply contrasts with cycloheptatriene (pK_a of ~ 36), where loss of the hydrogen would give the antiaromatic 8 π electron cycloheptatrienyl anion **290**.



6. *d*-Orbital effects^{320a} are important only when atoms are present that are not in the second row of the periodic chart, such as sulfur, phosphorus or transition metals. Carbanions can be stabilized by overlap of the electron pair with 3d orbitals of third row elements such as phosphorus and sulfur.³²⁸ Dithioacetal **291** is more acidic than acetal **292** by 5-6 pK_a units. The carbanionic p orbital aligns itself to minimize electrostatic repulsion, as in **293**.³²⁹ Forcing these orbitals into close proximity by confining them to a polycyclic system significantly decreases the acidity. Tris(sulfone) **294** is less acidic than **295**, but in this case solvation effects contribute to the difference in acidity.^{328,329}



In summary, all six factors described above contribute to the following order of acidity, based on the ability of that functional group to enhance the acidity of

 $NO_2 > CO > SO_2 > CO_2H > CO_2R \sim CN \sim C(=O)NH_2 > X > H > R$

The pK_a values of several common functional groups are presented in Table 8.16 to show the

^{327. (}a) Nickon, A.; Lambert, J.L. J. Am. Chem. Soc. 1962, 84, 4604; (b) Idem Ibid. 1966, 88, 1905.

^{328.} von E. Doering, W.; Hoffmann, A.K. J. Am. Chem. Soc. 1955, 77, 521.

^{329.} von E. Doering, W.; Levy, L.K. J. Am. Chem. Soc. 1955, 77, 509.
effect on acidity of carbonyl substituents in the context of other organic acids. In reactions with an appropriate acidic molecule, the organolithium reagent removes the acidic proton to give the new organolithium reagent. In general, an organolithium reagent will exchange with an acidic hydrogen of another molecule if the conjugate acid of the newly-formed organolithium reagent is a *weaker* acid than the original organolithium reagent. According to this rationale, methyllithium (pK_a of methane is 40) will remove the acidic hydrogen in phenylacetylene (pK_a is 21) (see Table 8.16). Metal-hydrogen exchange therefore generates a carbanion that can subsequently be used as a nucleophile in addition reactions, or for substitution reactions. Enolization of carbonyl derivatives is usually accomplished with lithium dialkylamide bases rather than alkyllithium reagents, as discussed in Section 9.2.B.

<u>ACID</u>	<u>pK</u> a	ACID	<u>pK</u> a	ACID	<u>pK</u> a	ACID	<u>pK</u> a
$\stackrel{\rm H}{\star} \stackrel{\rm NO_2}{\underline{\mathbf{H}}} _{\rm NO_2}$	3.6 ^a	H CN H CN	12 ^a	$\overset{O}{\overset{H}{\underset{H}}}_{\overset{H}{\underset{H}}}\overset{H}{\overset{H}{\underset{H}}}$	20.8 ^{d,e}	$\left< {}^{S}_{S} \times {}^{Ph}_{\underline{H}} \right.$	29.6 ^c
Ph-CO ₂ H	4.2 ^a		12.7 ^a		21 ^b	$\left< {}^{S}_{S} \times_{H}^{\underline{H}} \right.$	31.3°, 36.5 ⁱ
0 0 <u> </u>	4.7 ^b	$\underbrace{\mathbf{H}}_{\mathrm{K}}^{\mathrm{CO}_{2}\mathrm{Et}}_{\mathrm{CO}_{2}\mathrm{Et}}$	13.3ª	Ph-C=C- <u>H</u>	21 ^b	Ph ₃ C- <u>H</u>	32.5 ^b
Ме-СО <u>2Н</u>	4.8 ^b	$\frac{\mathbf{H}}{\mathbf{H}} \mathbf{x}_{SO_2Me}^{SO_2Me}$	14 ^a	→ Me H <u>H</u>	21.3 ^d	$\left< \overset{S}{\underset{S}{}} \overset{Ph}{\underline{H}} \right>$	34 ^c
н СНО н СНО <u>н</u> СНО	5.0 ^a	$\mathbb{S}_{\underline{\mathbf{H}}}^{\mathrm{H}}$	14-15 ^b	O H H	21.6 ^d	H ⊾ ^{Ph} ∐ Ph	35 ^b
О СНО <u>Ш</u>	5.9 ^a	$ \begin{array}{c} EtO_2C \\ \underline{\mathbf{H}} \\ Et \end{array} \begin{array}{c} CO_2Et \\ \underline{\mathbf{H}} \\ Et \end{array} $	15 ^a	Ph ₂ N– <u>H</u>	23 ^b	н № Н Н	35 ^b [41] ^f
	5.85 ^a	<u>Н</u> -ОН	15.7 ^b	Et ₂ N– <u>H</u>	23 ^b	${\color{black}}{}_{H}^{\underline{H}}$	36 ^b
$\stackrel{\mathrm{NO}_2}{{{\xrightarrow}}_{\mathrm{H}}} \underline{\mathrm{H}}$	8.6 ^a	$H_3C - O\underline{H}$	16 ^b	<u>H</u> ₃ C–SO ₂ Me	23 ^a	$H_{H} = C_{H}$	36.5 ^b [44] ^f
O O H H Ph	9.4 ^a		16.5ª	→ <u>H</u>	23.5 ^{d,e}	$\bigcirc^{\underline{H}}$	37 ^b [44] ^f
Me₃N– <u>H</u>	9.8 ^a	Et − O <u>H</u> <i>t</i> -Bu− O <u>H</u>	18 ^c	$\underline{\mathrm{H}}_{3}\mathrm{C-CO}_{2}\mathrm{H}$	24 ^g	$\left< {}^{\mathrm{S}}_{\mathrm{S}} \times {}^{\mathrm{Me}}_{\underline{\mathbf{H}}} \right.$	38.3 ^c
<u>с</u> -о <u>н</u>	9.9 ^{a,k}	Ph H H	18.6 ^{b,d}	H—C≡C— <u>H</u>	25 ^b	$\langle {}^{S}_{S} {}^{Et}_{\underline{H}}$	38.6 ^c
H-CH2NO2	10.2 ^a	Ph H H	19.1 ^d	<u>H</u> -CH ₂ CO ₂ Et	25.6 ^h	$\triangleright_{\mathrm{H}}^{\underline{\mathrm{H}}}$	30 ^b
_ ^{O-<u>H</u>}	10.5 ^j	$Ph \overset{O}{\underbrace{H}} Me \overset{Me}{\underbrace{H}} Me$	19.5 ^d	$\underline{\mathrm{H}}_{3}\mathrm{C}^{\mathrm{O}}_{\mathrm{NH}_{2}}$	25 ^a	<u>H</u> CH ₃	40 ^b
O O <u>H</u> Me	11 ^a	O H H	20 ^a	Ph-N <u>H</u> 2	27 ^b	$\bigcirc^{\rm H}_{\underline{\mathbf{H}}}$	45 ^b [51] ^f

Table 8.16. pK^a Values of Organic Acids

a Ref. ³³⁰ b Ref. ³³¹ c Ref. ³³² d Ref. ³³³ e Ref. ³³⁴ f Ref. ³³⁵ g Ref. 279 h Ref. ³³⁶ i Ref. ³³⁷ j Ref. ³³⁸ k Ref. ³³⁹

The acidities of several ketones have also been measured in DMSO.³⁴⁰

Metal-hydrogen exchange is useful for the preparation of allylic and alkyl^{330b}, aryl^{341a} or heteroaryl lithio derivatives. Several examples were used in previous syntheses, including the conversion of $239 \rightarrow 240$ and $245 \rightarrow 246$. Asymmetric deprotonation is possible using *sec*-butyllithium and (–)-sparteine (163, and see the reaction of 275 above). The reaction of Boc pyrrolidine derivative 296, for example, gave 297 and subsequent reaction with the methylating agent dimethyl sulfate gave a 45% yield of 298 in a ratio of 93:7 syn/anti diastereomers.³⁴² It is also possible to generate allyllithium derivatives from allylic hydrocarbons.³⁴³



The disconnections for the aryl substitution reactions are

 $Ar - CO_{2}H \swarrow Ar - H \quad ArCR_{2}OH \swarrow Ar - H + R_{2}C = O \quad Ar - CH_{2}R \swarrow Ar - H + R - CH_{2}X \quad RCH = C(R)CH_{2}R \swarrow RCH = C(R)CH_{3}RCH = C$

- 330. Pearson, R.G.; Dillon, R.L. J. Am. Chem. Soc. 1953, 75, 2439
- 331. Reference 49a, pp 4, 10, 13, 14, 43, 48.
- 332. Streitweiser, Jr., A.; Ewing, S.P. J. Am. Chem. Soc. 1975, 97, 190..
- 333. Zook, H.D.; Kelly, W.L.; Posey, I.Y. J. Org. Chem. 1968, 33, 3477.
- 334. House, H.O. Modern Synthetic Reactions, 2nd Ed. W.A. Benjamin, Menlo Park, CA., 1972, p 494.
- 335. (a) Streitwieser, Jr., A.; Caldwell, R.A.; Granger, M.R. J. Am. Chem. Soc. 1964, 86, 3578; (b) Streitwieser, Jr., A.; Maskornick, M.J.; Ziegler, G.R. Tetrahedron Lett. 1971, 3927.
- 336. Amyes, T.L.; Richard, J.P. J. Am. Chem. Soc. 1996, 118, 3129.
- 337. For acidity of 1,3-dithiane in DMSO, see Xie, L.; Bors, D.A.; Streitwieser, A. J. Org. Chem. 1992, 57, 4986.
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- 339. Liptak, M.D.; Gross, K.C.; Seybold, P.G.; Feldgus, S.; Shields, G.C. J. Am. Chem. Soc. 2002, 124, 6421.
- 340. Bordwell, F.G.; Harrelson, Jr., J.A. Can. J. Chem. 1990, 68, 1714.
- 341. (a) Letsinger, R.L.; Schnizer, A.W. J. Org. Chem. 1951, 16, 869; (b) Breslow, R.; Grant, J.L. J. Am. Chem. Soc. 1977, 99, 7745.
- 342. Wu, S.; Lee, S.; Beak, P. J. Am. Chem. Soc. 1996, 118, 716.
- 343. For a synthetic example taken from a synthesis of β-bisabolene, see Crawford, R.J.; Erman, W.F.; Broaddus, C.D. J. Am. Chem. Soc. 1972, 94, 4298.

MOLECULAR MODELING: Acidities of Carboxylic Acids

The electrostatic potential is the energy felt by a point positive charge at a location near a molecule. It balances the repulsion between the charge and the nuclei and the attraction between the charge and the electrons. Of more practical value is an electrostatic potential map. This presents the electrostatic potential at all locations on an electron density surface which, like a space-filling model, depicts the accessible area of a molecule. As such, an electrostatic potential map provides a measure of the distribution of charge on the surface. By convention, negatively charged regions on the surface are colored "red", positively charged regions are colored "blue" and neutral regions are colored "green".

There are many times in organic chemistry when knowing the relative acidity of two or more acids may be important issue, and pK_a values are not available in the literature. Here, electrostatic potential maps may provide a viable alternative. Do these correlate with acidity for series of related compounds? For example, does the (maximum) potential on the acidic hydrogen in carboxylic acids correlate with measured pK_a ? One after another, build four (or more) of the carboxylic acids from the following list. (After the first model, *click* on > at the top of the screen and select **Continue** to bring up a fresh builder without removing this text.) Calculate an electrostatic potential map for each of the four carboxylic acids and use a graphing program to make a plot of the value of the electrostatic potential at the acidic hydrogen vs. pK_a (given after the name). To "measure" the value of the screen.

trichloroacetic acid	0.7
oxalic acid	1.23
dichloroacetic acid	1.48
cyanoacetic acid	2.45
chloroacetic acid	2.85
fumaric acid	3.10
terephthalic acid	3.51
formic acid	3.75
(E)-3-chloroacrylic acid	3.79
benzoic acid	4.19
3-(p-chlorophenyl)-trans-acrylic acid	4.41
crotonic acid	4.70
acetic acid	4.75
pivalic acid	5.03

Based on the few compounds you have examined, are you able to conclude that electrostatic potentials at the acidic hydrogen correlate with the pKa's of carboxylic acids? Try to identify a carboxylic acid that is more acidic (smaller pKa) than trichloroacetic acid and use the best fit line you obtained to predict its pKa. Try to identify a carboxylic acid that is less acidic (larger pKa) than pivalic acid and predict its pKa.

8.6. SULFUR STABILIZED CARBANIONS AND UMPOLUNG

Introducing a heteroatom (X) into an organic molecule enhances the acidity of the proton adjacent to the heteroatom (H–C–X). A sulfur group makes the proton more acidic due to electron-withdrawing effects, as well as by stabilization of the resulting carbanion by the d orbitals (see above).^{328,329} Several different sulfur-stabilized carbanions are known, and have been used extensively in organic synthesis.^{344,345} Sulfur stabilized carbanions react with alkyl halides or with aldehydes and ketones in the same manner as other carbanions.

8.6.A. Sulfur Carbanions

Thioethers (sulfides)³⁴⁸ can be converted to their α -carbanion derivative (**299**, M = Li, Na, K) by treatment with strong bases such as *n*-butyllithium, sodium amide (NaNH₂) or potassium amide (KNH₂). The hydrogen atom α -to the sulfur atom of sulfides is a weaker acid than that the hydrogen atom α -to a carbonyl, nitrile or nitro group, and stronger bases are required for deprotonation. Sulfides are stronger acids, than the allylic, vinyl or aromatic hydrocarbons discussed above, however. The various oxides of sulfur, including sulfoxides (**300**), sulfones (**301**) or sulfonate esters (**302**) can be converted to α -carbanions. Increasing the number of oxygens on the sulfur atom generally increases the acidity of the α -proton. Bordwell and coworkers studied the acidity of several sulfur derivatives using DMSO as a solvent.^{346,48b} Anders and co-workers studied the structure of sulfur-stabilized allyllithium compounds in solution, and found that they were monomers in THF.³⁴⁷



^{344.} Reference 265a, pp 94-103.

^{345.} Block, E. Aldrichimica Acta 1978, 11, 51.

^{346. (}a) Reference 344, p 9; (b) Bordwell, F.G.; Algrim, D. J. Org. Chem. 1976, 41, 2507; (c) Bordwell, F.G.; Bares, J.J.; Bartmess, J.E.; McCollum, G.J.; van der Puy, M.; Vanier, N.R.; Matthews, W.S. Ibid. 1977, 42, 321; (d) Bordwell, F.G.; Bares, J.E.; Bartmess, J.E.; Drucker, G.E.; Gerhold, J.; McCollum, G.J.; van der Puy, M.; Vanier, N.R.; Matthews, W.S. Ibid. 1977, 42, 326; (e) Bordwell, F.G.; Matthews, W.S.; Vanier, N.R. J. Am. Chem. Soc. 1975, 97, 442; (f) Bordwell, F.G.; Bartmess, J.E.; Drucker, G.E.; Drucker, G.E.; Margolin, Z.; Matthews, W. Ibid. 1975, 97, 3226.

^{347.} Piffl, M.; Weston, J.; Günther, W.; Anders, E. J. Org. Chem. 2000, 65, 5942.

Oxidation of a sulfoxide to a sulfone places a second oxygen on sulfur (RSO₂R, sec. 3.9.A.iii), and this increases the relative acidity of the α -hydrogen. Dimethyl sulfone is more acidic than the corresponding sulfoxide (RSOR, DMSO) by 6.1 p K_a units. The presence of an electron-releasing methyl group (PhSO₂CH₃ versus PhSO₂CH₂CH₃)^{317c} causes a reduction of acidity by two p K_a units. As the group attached to the sulfur becomes more electron withdrawing, the acidity increases (Me₃CSO₂CH₃ = 30.3, MeSO₂CH₃ = 31.1, PhSO₂CH₃ = 29.0, CF₃SO₂CH₃ = 18.8).^{346c,g} A similar trend is observed for the thio-analogs of acetonitrile (Me₃CSCH₂CN = 22.9, Me₂CHSCH₂CN = 23.6, CH₃CH₂SCH₂CN = 24.0, CH₃SCH₂CN = 24.3, PhSCH₂CN = 20.9).^{346g} Two sulfur groups significantly increase the acidity of the proton (CH₃SO₂CH₃ = 31.1, CH₃CH₂SO₂CH₂SO₂CH₂CH₃ = 14.4, CH₃SCH₂SOCH₃ = 29.0),^{346g} and another electron withdrawing group leads to an increase in acidity (CH₃SO₂CH₂CN = 13.6, CH₃SCH₂CN = 24.3).^{346g}

As mentioned, the proton on the α -carbon of a sulfide is a very weak acid and its removal requires a strong base.³⁴⁸ Organolithium reagents are commonly used for this purpose. Phenylisopropyl sulfide (**303**) reacted with *tert*-butyllithium (THF, HMPA) to give the α -lithio derivative **304**. Alkyl sulfides often require addition of HMPA or TMEDA to facilitate Li-H exchange. Organolithium reagent **304** reacted with allyl bromide to give **305** in 87% yield, or with benzaldehyde to give **306** in 92% yield.³⁴⁹



There are many synthetic applications for sulfide carbanions. Sulfide **307** required the addition of DABCO to facilitate deprotonation by butyllithium, but the resulting anion coupled readily with allylic chloride **308** under these conditions to give **309**. The sulfide moiety was removed by a dissolving metal reduction (for example, see secs. 4.9.D, 4.9.F) to give dendrolasin **310**.^{349b} The ability to remove the sulfur after activating a carbon for nucleophilic attack is one of the most attractive features of organosulfur chemistry. Coupling of allylic halides and allylic thiocarbanions is sometimes called **Biellmann alkylation**.³⁵⁰ Intramolecular reactions occur readily and reaction with epoxides or alkyl halides is possible.

^{348. (}a) Gilman, H.; Beaber, N.J. J. Am. Chem. Soc. 1925, 47, 1449; (b) Ipatieff, N.N.; Pines, H.; Friedman, B.S. Ibid. 1938, 60, 2731; (c) Hurd, C.D.; Gershbein, L.L. Ibid. 1947, 69, 2328; (d) Campbell, J.R. J. Org. Chem. 1964, 29, 1830; (e) Kharasch, M.S.; Fuchs, C.F. Ibid. 1948, 13, 97.

^{349. (}a) Dolak, T.M.; Bryson, T.A. Tetrahedron Lett. 1977, 1961; (b) Kondo, K.; Matsumoto, M. Ibid. 1976, 391.

^{350. (}a) Biellmann, J.F.; Ducep, J.B. *Tetrahedron* **1971**, *27*, 5861; (b) Altman, L.J.; Ash, L.; Marson, S. Synthesis **1974**, 129; (c) Grieco, P.A.; Masaki, Y. J. Org. Chem. **1974**, *39*, 2135.



When a sulfide group is attached to the α -carbon of a molecule an electron-withdrawing group such as a carbonyl (the sulfide is β to the carbonyl), the acidity of the α -proton is greatly enhanced (see Table 8.16). When α -phenylthio- γ -butyrolactone (**311**) was treated with lithium diisopropylamide (LDA, sec. 9.2.B), the 2-lithio derivative was formed. Subsequent reaction with iodomethane gave **312**.³⁵¹ The sulfide was especially useful in this synthesis, since facile oxidation to the corresponding sulfoxide (**313**) and subsequent heating induced syn-elimination to alkene **314** (sec. 2.9.C.v). The sulfide-alkylation sequence can be applied to many systems, and in some cases highly functionalized molecules can be prepared.



Sulfoxide carbanions formed by deprotonation of sulfoxides are common in alkylation reactions.³⁵² Chiral sulfoxides (sec. 3.9.A.ii) are possible, and reacton of the corresponding organolithium derivatives with aldehydes or ketones generates diastereomeric products. Once the organolithium derivative is generated, the stereochemical integrity of the C–Li bond is remarkably stable, possibly due to interactions with the adjacent functional groups. Conversion of the asymmetric keto-sulfoxide (**315**) to the carbanion, followed by condensation with propanal gave an alcohol-sulfoxide. The sulfoxide group was removed by treatment with aluminum amalgam to complete the asymmetric synthesis of 3-hydroxyketone **316** in 67% yield and 64% ee.³⁵³ Note that *tert*-butylmagnesium bromide was used as the base. The reductive cleavage of the sulfoxide with aluminum amalgam (sec. 4.9.I) is one of the most common methods for removing a sulfur moiety.



^{351. (}a) Grieco, P.A.; Reap, J.J. *Tetrahedron Lett.* 1974, 1097; (b) for a different example, see Trost, B.M.; Salzmann, T.N. J. Org. Chem. 1975, 40, 148.

^{352.} Reference 344, pp 94-97.

^{353.} Schnedier, F.; Simon, R. Synthesis 1986, 582.

Another variation in sulfoxide reactivity is shown after an initial conversion of **317** to **318** via reaction with LDA and alkylation with methyl iodide.^{354b} In this case, removal of the sulfur moiety allowed formation of an allylic alcohol. Heating allylic sulfoxide **318** induced a facile [2,3]-sigmatropic rearrangement (sec. 11.12.A) to give **319**, and hydrolysis of **319** gave cyclohexenol derivative **320**. Trimethyl phosphite [P(OMe)₃] was added to trap a minor isomer of the equilibrium. This reaction is called the **Mislow-Evans rearrangement**.^{354,355} The [2,3]-sigmatropic rearrangement that occurs with allylic sulfoxides is useful and predictable, since it proceeds with high stereoselectivity.^{354c} This rearrangement is useful for introducing functional groups other than allylic alcohols into a molecule, as in Otera and co-worker's use of this reaction to generate conjugated aldehydes.³⁵⁶ Selenoxides also give this reaction.³⁵⁷



Sulfones are useful organosulfur compounds.³⁵⁸ In Yamada and co-worker's synthesis of cladocoran A,³⁵⁹ sulfone **321** was converted to the α -lithio compound by treatment with *n*-butyllithium. Subsequent reaction with 4-iodo-2-methyl-1-butene gave an 89% yield of sulfone **322**. Reduction of the sulfone with sodium amalgam gave a 91% yield of **323**. Note that sodium amalgam or Raney nickel [Ni(R)] are commonly used to remove sulfur from organic molecules (sec. 4.9.D).³⁶⁰ Reaction of a sulfone carbanion with an aldehyde, acetylation of the resulting alcohol, followed by elimination to an alkene is called **Julia olefination**.³⁶¹ In a synthesis of (–)-siccanin,³⁶² Trost and co-workers used this technique to convert sulfone **324** to **325** in 93% overall yield.

356. Sato, T.; Otera, J.; Nozaki, H. J. Org. Chem. 1989, 54, 2779.

- 359. Miyaoka, H.; Yamanishi, M.; Kajiwara, Y.; Yamada, Y. J. Org. Chem. 2003, 68, 3476.
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- 361. (a) Julia, M.; Paris J.M. *Tetrahedron Lett.* 1973, 14, 4833; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-50; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 356-357.
- 362. Trost, B.M.; Shen, H.C.; Surivet, J.-P. Angew. Chem. Int. Ed. 2003, 42, 3943.

^{354. (}a) Bickart, P.; Carson, F.W.; Jacobus, J.; Miller, E.G.; Mislow, K. J. Am. Chem. Soc. 1968, 90, 4869; (b) Evans, D.A.; Andrews, G.C. Acc. Chem. Res. 1974, 7, 147; (c) Hoffmann, R.W. Angew. Chemie. Int. Ed. 1979, 18, 563.

^{355. (}a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-62; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 430-431.

^{357.} For an example taken from a synthesis of pseudocodeine, see Kshirsagar, T.A.; Moe, S.T.; Portoghese, P.S. *J. Org. Chem.* **1998**, *63*, 1704.

^{358. (}a) Magnus, P.D. Tetrahedron 1977, 33, 2019; (b) Reference 344, pp 97-103.



In 1-lithio vinyl sulfides (sec. 8.6) the sulfur atom stabilizes the carbanionic center, allowing either alkylation or condensation reactions. Lithio vinyl sulfones are similarly stabilized. Vinyl sulfone (**326**), for example, was converted to the 1-lithio derivative with methyllithium.³⁶³ This organometallic reacted in the usual manner with alkyl halides (methyl iodide) to give the coupling product, **327**.



Vinyl sulfoxides undergo an unusual elimination reaction when a leaving group such as chloride is also present on the double bond. When **328** was treated with *tert*-butyllithium, exchange occurred to give **329**.³⁶⁴ In the presence of additional *tert*-butyllithium, chloride is lost and a lithio alkyne (**330**) is formed in what is known as the **Fritsch-Buttenberg-Wiechell rearrangement**.³⁶⁵ Hydrolysis led to the final product, alkyne **331**, in 74% yield. A similar reaction was observed when **328** was treated with Grignard reagents.



363. Eisch, J.J.; Galle, J.E. J. Org. Chem. 1979, 44, 3277, 3279.

364. Satoh, T.; Hayashi, Y.; Yamakawa, K. Bull. Chem. Soc. Jpn. 1993, 66, 1866.

365. (a) Fritsch, P. Annalen 1894, 279, 319; (b) Buttenberg, W.P. Annalen 1894, 279, 327; (c) Wiechell, H. Annalen 1894, 279, 332; (d) Stang, P.J. Chem. Rev. 1978, 78, 383; (e) Stang, P.J.; Fox, D.P. J. Org. Chem. 1978, 43, 364; (f) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-35; (g) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 262-263.

Formation of a carbanion is often accompanied by loss of the SO₂ moiety in α -halo sulfones, via the so-called **Ramberg-Bäcklund reaction**,³⁶⁶ as in the conversion of 1-bromoethyl ethyl sulfone (**332**) to 2-butene.³⁶⁷ Initial reaction with KOH generated the sulfone carbanion (**333**), which displaced bromide intramolecularly to give an episulfone (**334**). Under the reaction conditions, **334** lost sulfur dioxide (SO₂) to give the alkene. Meyers introduced a modification of this reaction in which the sulfone was converted directly to the alkene without isolating the α -halosulfone, using KOH in CCl₄.^{368,369} Sulfuryl chloride and bromine can also be used.³⁶⁹



Sulfonate carbanions have been used less extensively than sulfone, sulfoxide or sulfide carbanions. Sulfonates are good leaving groups and subject to nucleophilic displacement or elimination in the presence of the bases required to generate the carbanion. Cyclic sulfonates (sultones, **335**) have been alkylated³⁷⁰ via initial reaction with *n*-butyllithium and then an alkyl halide. Sultone **335** was used in Wolinsky and co-worker's synthesis of the terpene β-santalene (**337**), via alkylation with 1-bromo-3-methyl-2-butene to give **336**.³⁷¹ The sulfur was removed by reduction with aluminum hydride (AlH₃, sec. 4.6.B), and subsequent treatment with POCl₃ and pyridine generated the exo-methylene group (secs. 2.8.A, 2.9.A).³⁷¹ Note that reductive cleavage of the sultone can give the thioalcohol via S–O cleavage and/or the alcohol via C–O cleavage.^{370a} Sultones and sulfonate esters are rarely used in synthesis, but sulfides and sulfones are common.



^{366. (}a) Ramberg, L.; Bäcklund, B. Arkiv. Kemi Mineral. Geol. 1940, 13A, 50 [Chem. Abstr. 34: 47255, 1940];
(b) Paquette, L.A. Acc. Chem. Res. 1968, 1, 209; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-77; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 540-541.

- (a) Pommelet, J.-C.; Nyns, C.; Lahousse, F.; Morény, R.; Viehe, H.G. Angew. Chemie. Int. Ed. 1981, 20, 585; (b) Martel, H.J.J.-B.; Rasmussen, M. Tetrahedron Lett. 1975, 947.
- 370. (a) Smith, M.B.; Wolinsky, J.J. Org. Chem. 1981, 46, 101; (b) Durst, T.; Tin, K.C. Can. J. Chem. 1970, 48, 845.
- 371. (a) Wolinsky, J.; Marhenke, R.L.; Eustace, E.J. J. Org. Chem. 1973, 38, 1428; (b) Coffen, D.L.; Grant, B.D.; Williams, D.L. Int. J. Sulfur Chem., Part A 1971, 1, 13.

^{367. (}a) Block, E. *Reactions of Organosulfur Compounds*, Academic Press, New York, *1978*; (b) Block, E. J. *Chem. Educ. 1971*, *48*, 814; (c) Paquette, L.A., *Org. React. 1977*, *25*, 1; (d) Bordwell, F.G.; Jarvis, B.B.; Corfield, P.W.R. J. Am. Chem. Soc. *1968*, *90*, 5298; (e) Paquette, L.A.; Philips, J.C. *Ibid. 1969*, *91*, 3973; (f) Paquette, L.A.; Houser, K.W. *Ibid. 1969*, *91*, 3870; (g) Corey, E.J.; Block, E. J. Org. Chem. *1969*, *34*, 1233.

^{368.} Meyers, C.Y.; Malte, A.M.; Matthews, W.S. J. Am. Chem. Soc. 1969, 91, 7510.

MOLECULAR MODELING: Relative CH Acidities of Sulfur Compounds

The absolute acidity of a molecule is the energy required to remove a proton.

 $\mathrm{R-}\mathrm{H} \longrightarrow \mathrm{R^-} + \mathrm{H^+}$

As it turns out, it is very difficult to accurately calculate absolute acidity (and impossible to actually measure such a quantity). However, even simple quantum chemical methods provide a reasonable account of the relative acidities of closely related compounds.

Obtain an electrostatic potential map for phenyl methyl sulfoxide. This colors an electron density surface (revealing the overall size and shape) with the energy that a positive charge "feels" at various locations on the surface. By convention, positive regions (where the charge is repelled) are colored "blue" and negative regions (where the charge is attracted) are colored "red". Acidic sites will be blue. Identify these regions on the map and record the value of the potential. (*Click* on the region and the value of the potential will be displayed at the bottom of the screen.) Repeat your calculations for phenyl methyl sulfone and phenyl methyl sulfide. For each new structure, *click* on > to the right of the tab at the top of the screen and select *Continue*. According to electrostatic potential maps, which compound is most acidic and which is least acidic?

Next calculate energies for the two reactions shown below (comparing acidities of phenyl methyl sulfoxide and phenyl methyl sulfone with that of phenyl methyl sulfide as a standard).

Ph–SO–CH₃ + Ph–S–CH₂⁻ → Ph–SO–CH₂⁻ + Ph–S–CH₃ Ph–SO₂–CH₃ + Ph–S–CH₂⁻ → Ph–SO₂–CH₂⁻ + Ph–S–CH₃

You have already calculated energies for the three neutral molecules, so you only need to obtain energies for the three anions. Work out energies of the two reactions. Are both the sulfoxide and the sulfone stronger acids than the sulfide? Which is the stronger acid, the sulfoxide or the sulfone?

Repeat your calculations for 1,3-dithiolane and for 1,3-dithiane. Which protons in 1,3-dithiolane and which in 1,3-dithiane are more acidic?



The disconnections for these reactions found in this section are



8.6.B. Umpolung

We are used to seeing a certain kind of reactivity associated with a given functional group. In some cases, it is possible to reverse the reactivity, in effect making an electrophilic center in to a nucleophilic one and vice versa. This section will explore reactions that allow this reversal.



8.6.B.i. Definition of Umpolung. Under normal conditions, a carbonyl group is polarized as shown in **338**, with the carbonyl carbon electrophilic and the a-carbon nucleophilic. Facile formation of an enolate anion (see **280**) demonstrates this bond polarization. In a hypothetical **339** the acyl carbon

would be nucleophilic, but to attain this reversal the carbonyl must be transformed into another functional group that allows the carbon to become nucleophilic. The ability to regenerate the carbonyl after completion of the desired reactions is another requirement. Seebach termed this process **umpolung**.³⁷² There is umpolung (reversal of reactivity) whenever one observes a 1,2-*n* relationship of the functional groups in a carbonyl compound, where *n* is the number of carbon atoms separate the carbons bearing the functional groups. For Umpolung to occur, an even number of carbons should separate the carbons bearing the functional groups (0, 2, 4, ... as in **345**, where no carbons separate the groups, and in **346** where two carbons separate the groups).^{372a} This relationship contrasts with normal reactivity, where an odd number of carbons separate the groups (1, 3, 5, ... as **347** where one carbon separates the groups, and in **348** where three carbons separate the groups).^{372a} Table 8.17^{372c} shows several umpolung equivalents, along with the reactivity of the normal fragment and typical reagents that give the umpolung reactivity.



 Table 8.17. Typical Umpolung Equivalents and Reagents

372. (a) Seebach, D. Angew. Chem. Int. Ed. 1979, 18, 239; (b) Seebach, D. Ibid. 1969, 8, 639; (c) Gröbel, B.-T.; Seebach, D. Synthesis 1977, 357; (d) Seebach, D.; Kolb, M. Chem. Ind. (London) 1974, 687.



8.6.B.ii. Acyl Anion Equivalents. The most common umpolung equivalent is that for acyl anion **340**, and dithianes derived from aldehydes (**349**) are the most common reagent used for this purpose. Dithianes are available from ketones, and this is a common ketone protecting group (sec. 7.3.B.ii), but no hydrogen is available for removable. 1,3-Propanedithiol is the usual precursor for the preparation of **349**. Note that a nonthiolic, odorless equivalent has been reported.³⁷³ Removal of the hydrogen adjacent to the sulfur in **349** requires a base such as *n*-butyllithium, and the product is α -lithiodithiane (**350**). The acidity of this hydrogen is largely due to greater polarizability of the sulfur, and the greater C–S bond length, rather than to the presence of the d orbitals.³⁷⁴ The pK_a of 1,3-dithiane (**349**, R = H) is 31.1.³³⁵ 2-Methyl-1,3-dithiane (**349**, R = Me) has a pK_a of 38.3, however, whereas 2-phenyl-1,3-dithiane (**349**, R = Ph) has a pK_a of 29.6.³⁰⁷ The acidity is clearly dependent on

the electronic effect of the substituent. There are many dithioacetal derivatives (remember that dithioketals do not posses an acidic hydrogen), including both acyclic and cyclic species. For reasons of stability, availability and ease of preparation, dithianes are used most often.

A typical application is the reaction of 1,3-dithiane with an aldehyde to give **351** in 92% yield, taken from the synthesis of amphidinolide T3 by Zhao and co-workers.³⁷⁵ Subsequent treatment of *tert*-butyllithium, and reaction with iodide shown gave **352** in 83% yield. To complete the reversal of reactivity, the carbonyl must be unmasked, which is usually done by reaction with a Lewis acid that has a high affinity for sulfur, such as mercuric oxide with boron trifluoride in aqueous THF.³⁷⁶ In this particular example, treatment of **352** with iodine and sodium bicarbonate in aqueous acetone gave an 82% yield of **353**.³⁷⁵ Many different oxidants have been employed to unmask dithianes, including Cl₂, Br₂, *t*-BuOCl, NBS, Pb(OAc)₄, Ce(NH₃)₆(NO₃)₄, Tl(O₂CCF₃)₃, and so on.³⁷⁷ The choice of reagent depends on the facility of the hydrolysis and the sensitivity of the molecule to further reaction. Dithianes are widely used in natural product synthesis.³⁷⁸

- 376. (a) Seebach, D.; Corey, E.J. J. Org. Chem. 1975, 40, 231; (b) Seebach, D. Synthesis 1969, 17.
- 377. Romanet, R.F.; Schlessinger, R.H. J. Am. Chem. Soc. 1974, 96, 3701.
- 378. Yus, M.; Nájera, C.; Foubelo, F. Tetrahedron 2003, 59, 6147.

^{373.} Liu, Q.; Che, G.; Yu, H.; Liu, Y.; Zhang, J.; Zhang, Q.; Dong, D. J. Org. Chem. 2003, 68, 9148.

^{374.} Bernardi, F.; Csizmadia, I.G.; Mangini, A.; Schlegel, H.B.; Whangbo, M.H.; Wolfe, S. J. Am. Chem. Soc. 1975, 97, 2209.

^{375.} Deng, L.-S.; Huang, X.-P.; Zhao, G. J. Org. Chem. 2006, 71, 4625.



Lithiated dithianes react best with primary and secondary alkyl halides,³⁷⁹ acyl halides, ketones and aldehydes,³⁸⁰ as well as epoxides.³⁸¹ Nitriles and amides react only if there is no acidic proton. An important synthetic use of this reaction is the preparation of highly functionalized aldehydes using **349** (R = H) as a starting material.³⁸² This is an important route to β -hydroxy and alkoxy aldehydes, and many substituents can be incorporated.

The disconnection for the acyl anion umpolung is

$$\begin{array}{|c|c|c|} O \\ R \stackrel{O}{\longrightarrow} R^{-} CHO + R^{1} - X \end{array}$$

Dithiane anions can be used in more creative ways, and with electrophilic species such as epoxides. In the construction of an advanced intermediate of spongistatin,³⁸³ Smith and co-worker's reacted 2-silyl dithiane **354** with *tert*-butyllithium to form the 2-lithio species. Subsequent reaction with epoxide **355** and then epoxide **356** led to initial coupling, followed by *in situ* loss of the silyl unit to allow coupling of the second epoxide giving a 69% yield of **357**. Smith termed this sequence a "linchpin assembly",³⁸⁴ and the dithiane unit was converted to the ketone later in the synthesis. This two-directional approach was used with halides in Stockman and co-worker's synthesis of perhydrohistrionicotoxin.³⁸⁵ 1,3-Dithiane was treated with butyllithium and then with halide **358**. This sequence was followed by a second round of butyllithium and then **358**, giving **359** in an overall yield of 70%. Later in this synthesis, the dithiane moiety was converted to the ketone by treatment with NCS and silver nitrate in aqueous acetonitrile.³⁸⁵



- Corey, E.J.; Andersen, N.H.; Carlson, R.M.; Paust, J.; Vedejs, E.; Vlattas, I.; Winter, R.E.K. J. Am. Chem. Soc. 1968, 90, 3245.
- (a) Corey, E.J.; Weigel, L.O.; Chamberlin, A.R.; Lipshutz, B. J. Am. Chem. Soc. 1980, 102, 1439; (b) Corey, E.J.; Weigel, L.O.; Floyd, D.; Bock, M.G. Ibid. 1978, 100, 2916.
- 381. Corey, E.J.; Bock, M.G. Tetrahedron Lett. 1975, 2643.
- 382. Vedejs, E.; Fuchs, P.L. J. Org. Chem. 1971, 36, 366.
- 383. SmithIII, A.B.; Doughty, V.A.; Sfouggatakis, C.; Bennett, C.S.; Koyanagi, J.; Takeuchi, M. Org. Lett. 2002, 4, 783.
- 384. Smith III, A.B.; Pitram, S.M.; Boldi, A.M.; Gaunt, M.J.; Sfouggatakis, C.; Moser, W.H. J. Am. Chem. Soc. 2003, 125, 14435.
- 385. Stockman, R.A.; Sinclair, A.; Arini, L.G.; Szeto, P.; Hughes, D.L. J. Org. Chem. 2004, 69, 1598.

Although conjugate addition is known, dithiane anions most often give 1,2-addition with conjugated systems. Cyclohexenone reacted with **350** (R = Me) to give the 1,2-addition product **360** in 99% yield.³⁸⁶ In this case, treatment with aqueous acid led to a rearrangement that gave **361** in 83% yield. Unmasking the carbonyl with mercuric salts led to an 80% yield of **362**.³⁸⁶ With stabilized carbanions of this type, 1,4-addition products are observed in some cases, but this may be due to a kinetic-thermodynamic phenomenon in which the initially formed 1,2-addition product equilibrates to a 1,4-adduct.³⁸⁷ This equilibration can be induced by treatment with base. For example, Wilson and co-workers showed that treatment of **360** with 1-1.5 equivalents of KH in HMPA/THF led to a 23% yield of the 1,4-adduct (the 3-dithianylcyclohexanore).³⁸⁸ The extent of 1,2- versus 1,4-addition observed is dependent on the reaction conditions employed.



As mentioned above, many reagents have been used for hydrolysis, which in part is due to variations in reactivity of the dithiane as the nature of the 2-alkyl group changes. Several problems can arise during hydrolysis. The reaction becomes acidic so BaCO₃, CaCO₃ or HgO are often added to maintain neutrality. Hydrolysis of dithianes derived from aldehydes often give acetals in neutral media. When an alkenyl group is present, addition of mercuric ion can give a competitive oxymercuration reaction (sec. 2.10.B). In general, HgO/BF₃•OEt₂ in aqueous organic solvents is used for hydrolysis of sensitive substrates.³⁸⁶

Acyl anion equivalents are not limited to dithianes, and virtually any dithioacetal can be used. Another common reagent is dithiolane (363),³⁸⁹ prepared from an aldehyde and 1,2-ethanedithiol. A dithiolane such as 363 reacts with organolithium reagents to give 2-lithio-1,3-dithiolane derivative 364, and reaction with an alkyl halide in the usual manner generates

^{386. (}a) Corey, E.J.; Seebach, D. Angew. Chem. Int. Ed. 1965, 4, 1075, 1077; (b) Corey, E.J.; Crouse, D. J. Org. Chem. 1968, 33, 298.

 ^{387. (}a) Schultz, A.G.; Yee, Y.K. J. Org. Chem. 1976, 41, 4044; (b) Deschamps, B.; Anh, N.T.; Seyden-Penne, J. Tetrahedron Lett. 1973, 527; (c) Luchetti, J.; Krief, A. Ibid. 1978, 2697; (d) Still, W.C.; Mitra, A. Ibid. 1978, 2659.

^{388. (}a) Wilson, S.R.; Misra, R.N.; Georgiadis, G.M. J. Org. Chem. 1980, 45, 2460; (b) Wilson, S.R.; Misra, R.N. Ibid. 1978, 43, 4903.

^{389.} Herrmann, J.L.; Richman, J.E.; Schlessinger, R.H. Tetrahedron Lett. 1973, 2599.

365. The reaction conditions are important since lithio dithiolanes such as **364** can fragment (see below). For this reason, dithiane derivatives are more commonly used as umpolung reagents as mentioned above. The same reagents that unmasked a dithiane to give back a carbonyl will convert a dithiolane to a carbonyl. Other reagents that function as acyl anion equivalents include **366**,³⁹⁰ **367**,³⁹¹ and **368**.³⁹²



Schlessinger and co-workers used a mixed sulfide-sulfoxide derivative (**369**) to achieve the umpolung. The advantages of this reagent include ease of generation (the proton is more acidic and NaH, KH, LDA can be used), greater stability of the anion and lower cost. Since the anion is more stable it is less reactive, and the alkylation reactions generally require higher temperatures.³⁹³ The diethyl



derivative is superior to the dimethyl.³⁹⁴ Acid hydrolysis is more facile, which is important since dithiane hydrolysis can be sluggish with highly substituted derivatives. The lithio-derivative **369** gave primarily Michael addition (1,4- or conjugate addition) in conjugated systems rather than the 1,2-addition usually observed with dithiane anions.³⁹⁵ These examples are meant to show there are many possible acyl anion equivalents. The exotic reagents are used to fine-tune an umpolung reaction when other reagents are unsatisfactory. In general, relatively simple dithiane and dithiolane derivatives are used.

A major drawback to using dithiolane anions is their relative instability when compared with dithiane anions (see discussion of **360**, see above). Lithio-dithiolanes are stable only when R in **364** is an anion stabilizing group such as COR or CO_2R , but when used in conjunction with such electron-withdrawing groups, the dithiolane becomes very useful.

Enol ethers such as methyl 1-propenyl ether (1-methoxypropene, **370**) constitute a second major class of acyl anion equivalents. When **370** was treated with *tert*-butyllithium (note the need for a stronger base with the less acidic vinyl hydrogen) and then condensed with benzaldehyde, the product was **371**.³⁹⁶ Lithiation of vinyl derivatives was described in Section 8.5. Facile

- 395. Herrmann, J.L.; Richman, J.E.; Schlessinger, R.H. Tetrahedron Lett. 1973, 3271.
- 396. Baldwin, J.E.; Höfle, G.; Lever, Jr., O.W. J. Am. Chem. Soc. 1974, 96, 7125.

^{390. (}a) Hackett, S.; Livinghouse, T. J. Org. Chem. 1986, 51, 879, 1629; (b) Trost, B.M.; Miller, C.H. J. Am. Chem. Soc. 1975, 97, 7182.

^{391.} Trost, B.M.; Salzmann, T.N. J. Am. Chem. Soc. 1973, 95, 6840.

^{392. (}a) Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G. J. Am. Chem. Soc. 1975, 97, 596; (b) Carey, F.A.; Hernandez, O. J. Org. Chem. 1973, 38, 2670.

^{393. (}a) Richmann, J.E.; Herrmann, J.L.; Schlessinger, R.H. *Tetrahedron Lett.* 1973, 3267; (b) Ogura, K.; Tsuchihashi, G. *Ibid.* 1971, 3151.

^{394.} Carlson, R.M.; Helquist, P.M. J. Org. Chem. 1968, 33, 2596.

hydrolysis with aqueous acid liberated the corresponding ketone (**372**), completing the acyl anion equivalency. Schlosser and co-workers found that a mixture of *sec*-butyllithium and potassium *tert*-butoxide could be used to generate the lithium anion of *O*-tetrahydropyranyl enol ethers.³⁹⁷ This modification generates a product that is more easily hydrolyzed to the ketone.



Vinyl sulfides can also function as acyl anion equivalents, but their preparation has not as yet been discussed. Wittig reagent such as **373** (sec. 8.8.A) reacted with benzenesulfenyl chloride to produce a new ylid (**374**), which condensed with benzaldehyde to give a 79% yield of the vinyl sulfide, **375**.³⁹⁸ When **375** was treated with mercuric salts, a 73% yield of phenylacetone was obtained. In the second approach, a vinyltin compound (**376**)³⁹⁹ was treated with methyllithium, and lithium-metal exchange provided **377**.²⁶⁹ Alkylation with iodomethane gave a 91% yield of **378**, and treatment with titanium tetrachloride led to a 75% yield of 1,1-diphenylacetone.²⁶⁹



In both cases, sulfur stabilized the lithium derivative and reaction with alkyl halides proceeded in a manner analogous to other vinyllithium reagents. Hydrolysis required mercuric salts or another Lewis acid to give the ketone, as in the preparation of Ph₂CHCOMe from **378**. Another preparation involves direct treatment of an alkylvinyl sulfide, such as ethylvinyl sulfide, with *sec*-butyllithium to give alkenyllithium (**379**). Subsequent treatment with an alkyl halide such as 1-bromooctane led to **380**, and hydrolysis with mercuric⁴⁰⁰ (see sec. 7.3.B.ii for a related reaction with dithioketals and dithioacetals) gave ketone **381** in 90% yield.



^{397.} Hartmann, J.; Stähle, M.; Schlosser, M. Synthesis 1974, 888.

^{398. (}a) Corey, E.J.; Seebach, D. J. Org. Chem. 1966, 31, 4097; (b) Carey, F.A.; Court, A.S. Ibid. 1972, 37, 939.

^{399.} For another synthetic example using stannane derivatives, see Hanessian, S.; Martin, M.; Desai, R.C. J. Chem. Soc. Chem. Commun. 1986, 926.

^{400.} Oshima, K.; Shimoji, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. J. Am. Chem. Soc. 1973, 95, 2694.

The disconnection for vinyl sulfides and enol ethers is

$$\begin{array}{c} O \\ R \\ \hline \\ R \\ \hline \\ R \\ \hline \\ R^1 \\ \hline \\$$

8.6.B.iii. A R(CO)CH₂⁺ Umpolung Equivalent. Reagents that reverse the usual nucleophilic character of the α -carbon to give 341 (see Table 8.17) are ketene dithioacetals (see 386, 388, and 392 below). These compounds can be prepared by several synthetic routes One of the more useful preparations is the Peterson olefination,⁴⁰¹ which is an alternative to the Wittig reaction (sec. 8.8.A) in which either trimethylsilylmethyllithium (382, X = Li) or its Grignard analog (X = MgBr, MgCl, etc.) reacts with aldehydes or ketones to give a β -silyl alcohol (383). Subsequent treatment with base induces elimination of the hydroxyl and the silyl group to give an alkene (in this case 1,1-diphenylethene, 384).⁴⁰¹ Ketene dithioacetals can be prepared by Peterson olefination, as in the reaction of 2-trimethylsilyl-1,3-dithiane (385) with *n*-butyllithium, followed by reaction with an aldehyde (such as isobutyraldehyde to give 386 in 44% yield).⁴⁰²



Dithiocarboxylic acid derivatives also provide a useful route to dithioketene acetals (another name for ketene dithioacetals).⁴⁰³ Treatment of dithiopropionic acid (**387**) with excess lithium diisopropylamide (LDA, for *O*-alkylation reactions see sec. 9.3.B), followed by reaction with excess iodoethane led to a 97% yield of ketene dithioacetal **388**.⁴⁰⁴ Ketene dithioacetals can be prepared by reaction of an aldehyde or ketone with dithioalkyl phosphonate esters such as **389**, which gave excellent yields of the dithioketene acetal upon reaction with aldehydes or ketones.⁴⁰⁵ Reaction of **389** with acetophenone, for example, gave **390** in 81% yield. Corey and Märkl showed that phosphonate ylids such as **391** also react with compounds such as

^{401. (}a) Peterson, D.J. J. Org. Chem. 1968, 33, 780; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-71; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 496-497.

 ^{402. (}a) Carey, F.A.; Court, A.C. J. Org. Chem. 1972, 37, 1926; (b) Trost, B.M.; Kunz, R.A. J. Am. Chem. Soc. 1975, 97, 7152;

^{403.} Beiner, J.M.; Thuillier, A. C.R. Acad. Sci., Ser. C 1972, 274,642.

^{404.} Ziegler, F.E.; Chan, C.M. J. Org. Chem. 1978, 43, 3065.

Mikolajczyk, M.; Grzejszczark, S.; Zatorski, A.; Mlotkowska, B.; Gross, H.; Costisella, B. Tetrahedron 1978, 34, 3081.

benzaldehyde to give the desired product, in that case 392.406



The actual umpolung reaction that allows a ketene dithioacetal to function as if it had an electrophilic carbon α to a carbonyl is achieved by conjugate addition of nucleophiles to the ketene dithioacetal, followed by hydrolysis. Both sulfide and sulfoxide ketene derivatives can be used. Conjugate addition of an ester enolate derived from *tert*-butyl acetate (secs. 9.2, 9.4.B, 9.7.A) to the ketene dithioacetal [CH₂=C(SOMe)₂] gave the stable dithioacetal anion (**393**). Conversion of the dithioacetal to the bis(sulfoxide) enhanced the ability of that species to function as a Michael acceptor. Subsequent transformation of **393** gave the aldehyde-ester (**394**).⁴⁰⁷



The disconnection for this process is:

8.6.B.iv. $R(CO)CH_2CH_2^-$ Umpolung Equivalents. In this umpolung equivalent (342, see Table 8.17), the reactive center is more distant from the carbonyl, making it more difficult to generate the umpolung reagent. Ketene dithioacetals can be used for the umpolung equivalent of 342, although the yields tend to be low. When the ketene dithioacetal possesses an allylic hydrogen (as in 395), treatment with a strong base generates a resonance-stabilized anion (396). Alkylation with an appropriate reagent (E–X) generates two products (398 and 399) from each of the two carbanionic centers. Two sulfur atoms stabilize the carbanion in 396, so 399 usually predominates unless R² in 395 is an electron withdrawing group. In that case, 396A may be stabilized to a greater extent giving 398 as the major product. Hydrolysis of 399 generates 400. Only 398 will yield the umpolung product (397) upon hydrolysis, suggesting that the umpolung is observed as the major process only when R² is an electron-withdrawing

^{406. (}a) Corey, E.J.; Märkl, G. Tetrahedron Lett. 1967, 3201; (b) Lemal, D.M.; Banitt, E.H. Ibid. 1964, 245.

^{407.} Herrmann, J.L.; Kieczykowski, G.R.; Romanet, R.F.; Wepplo, P.J.; Schlessinger, R.H. Tetrahedron Lett. 1973, 4711.

group. These principles are illustrated by the reaction of the ketene dithioacetal (**395**) with *n*-butyllithium to give a resonance-stabilized anion, which could be alkylated at either the α - (**399**) or the γ -position (**398**).^{372c,408} When R² = alkyl, the anion adjacent to the sulfur atoms is the most prevalent and dominates alkylation reactions. As mentioned above, the desired umpolung equivalent is obtained only when the anion (which gives **398**) is stabilized by electron-withdrawing groups at R², or when a hindered electrophile is used.⁴⁰⁸ When R² is cyano, the major product was **398**, but when R² was *n*-propyl, the major product was **399**.⁴⁰⁸



A more efficient method to generate this umpolung equivalent is via the dianion of allylic thiols. Treatment of allylthiol (2-propene-1-thiol, **401**) with base removes the acidic S–H hydrogen, and a second equivalent of strong base removes the hydrogen from the α -carbon to give **402**. The course of the subsequent alkylation reaction depends on the metal counterion of the base.⁴⁰⁹ When M = Li (from *n*-butyllithium) alkylation occurred at both the α and γ carbanionic centers (to give **404** and **405**, respectively), but γ -alkylation predominated (a 68:31 mixture favoring **404** in 93% yield).^{409,410} When M = Mg (magnesium *tert*-butoxide was added to effect the Li–Mg exchange reaction), substitution occurred predominantly at the carbon α to sulfur, giving **403**.⁴¹¹ Hydrolysis of **404** with mercuric salts liberated the aldehyde. There is a great preference for reaction at the α -position unless that position is sterically hindered. The solvent, the nature of the R group on sulfur and the nature of the electrophile play a role. Allylic sulfides are used more often than allylic thiols. The monoanion derived from an allylic sulfide also gives α and γ substitution.^{412,354b}

^{408.} Meyers, A.I.; Nolen, R.L.; Collington, E.W.; Narwid, T.A.; Strickland, R.C. J. Org. Chem. 1973, 38, 1974.

^{409.} Geiss, K.-H.; Seuring, B.; Pieter, R.; Seebach, D. Angew. Chem. Int. Ed. 1974, 13, 479.

^{410.} Hartmann, J.; Muthukrishnan, K.; Schlosser, M. Helv. Chim. Acta 1974, 57, 2261.

^{411.} Seebach, D.; Geiss, K.-H.; Pohmakotr, M. Angew. Chem. Int. Ed. 1976, 15, 437.

^{412.} Atlani, P.M.; Biellmann, J.F.; Dube, S.; Vicens, J.J. Tetrahedron Lett. 1974, 2665.



In the solvent THF, γ -substitution predominated in reactions of **402**, and addition of DABCO increased that yield, presumably by coordination near the sulfur to sterically block that position. Addition of HMPA favors more α -substitution, and addition of a strongly coordinating species such as a cryptate blocks the γ -position, which leads to α -substitution as the sole product.

Reasonable disconnections for this process are

$$\begin{bmatrix} 0 & R^1 & \square & 0 \\ R & \square & \square & R & R^1 - X \\ R & \square & R & R^1 & \square & R^1 \\ R^1 & \square & R^1 & \square & R^1 \\ R^1 &$$

8.6.B.v. A R(C=O)CH₂CH₂CH₂⁺ Equivalent. In this umpolung equivalent, the potentially positive center is even further removed from the carbonyl (see **343** in Table 8.17). This umpolung equivalent is best achieved by reaction of a nucleophile with a vinylogous ketene dithioacetal such as **406**.⁴¹³ Initial reaction of **406** with *n*-butyllithium proceeds via Michael type addition rather than deprotonation (there are no acidic hydrogens) to give the ketene dithioacetal anion (**407**). In order to achieve this umpolung equivalent, the ketene dithioacetal *cannot* have an acidic hydrogen present in the dithioacetal unit, since it would be selectively deprotonated. Addition of an alkyl halide such as iodomethane leads to alkylation at the dithiane carbon (to give **408**), and hydrolysis of the dithiane with mercuric chloride leads to the conjugated ketone **409**.⁴¹³ As mentioned earlier, this umpolung reagent is somewhat limited in utility because it cannot have acidic hydrogen atoms elsewhere in the molecule. It is important to mention what is becoming a pattern. As the umpolung center is removed further from the carbonyl, preparation of the requisite reagents becomes more difficult.



$$R \xrightarrow{O} R^1 \longrightarrow R^-X + \xrightarrow{CHO} R^1 - X$$

^{413.} Seebach, D.; Kolb, M.; Gröbel, B.-T. Angew. Chem. Int. Ed. 1973, 12, 69.

8.6.B.vi. An R(C=O)CH₂CH₂CH₂CH₂CH₂⁻ Equivalent. The final umpolung equivalent in Table 8.17 is 344, where the reactive center is separated from the carbonyl by three carbons. This umpolung equivalent is relatively easy to obtain, however, by the use of an allyl vinyl sulfide such as 410. Upon heating, a thio-Claisen rearrangement (sec. 11.12.D.iii) accomplishes the desired umpolung transformation.⁴¹⁴ A generalized example is treatment of 410 with base, followed by quenching with an electrophile (E⁺) to give 411. Heating leads to a thio-Claisen rearrangement and formation of thiocarbonyl derivative 412. Subsequent hydrolysis converts the thiocarbonyl to the carbonyl unit in 413. A simple example is the reaction of allyl vinyl sulfide 414 with *sec*-butyllithium to give the reactive α -lithio sulfide, and this reacted with benzyl bromide to give 415. Heating in aqueous dimethoxyethane led to the thio-Claisen product 416, and hydrolysis provided aldehyde 417 in 62% overall yield.⁴¹⁵ The specificity for the trans alkene in 416 arises from the chair-like transition state (see 415, secs. 11.12.C, 11.12.D), in which the benzyl group is equatorial in the lowest energy conformation leading to product.



The disconnection for this Umpolung is:

The ability to alter normal reactivity patterns of carbonyl derivatives allows a variety of carboncarbon bond forming processes to proceed. The products derived from these reactions can often be obtained by no other route and provide great flexibility in synthetic planning.

8.7 ORGANOCOPPER REAGENTS (C-Cu)

In all previous sections, the C^d reagent used as a nucleophilic source of carbon was an organometallic derived from sodium, potassium, magnesium or lithium reagents. In this section the focus will be on a class of reagents that contains a carbon-copper bond, the lithium

^{414.} Corey, E.J.; Shulman, J.I. J. Am. Chem. Soc. 1970, 92, 5522.

^{415.} Oshima, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. J. Am. Chem. Soc. 1973, 95, 2693.

dialkylcuprates (R'2CuLi).

2 *n*-BuLi + Cu^II
$$\xrightarrow{\text{ether}}$$
 Bu₂CuLi

8.7.A. Lithium Dialkylcuprates

8.7.A.i. Preparation of Gilman Reagents. Gilman et al. first observed that reaction of cuprous salts with two equivalents of an organolithium reagent generated an organocuprate such as lithium di-*n*-butylcuprate (Bu₂CuLi).^{416,94} The reagent formed is usually called a **Gilman reagent**, and is drawn as R₂CuLi.^{416,94} The mechanism⁴¹⁷ of the reaction probably involves an intermediate and conversion of a Cu(I) species to a transient Cu(III) species, and it may proceed via one-electron transfer.⁴¹⁸ The stability of organocopper species varies considerably with their structure. Whitesides and House⁴¹⁹ showed that dimethylcuprate (Me₂CuLi) was stable in ether for hours, at 0°C under nitrogen. Secondary and tertiary cuprates, however, rapidly decompose in ether above -20° C.⁴¹⁹ Disproportionation is the primary decomposition route for organocuprates, and the halide also plays a role in the stability of the cuprate. Cuprous iodide gives better results than cuprous bromide,⁴¹⁹ but the dimethyl sulfide-cuprous bromide complex (Me₂S•CuBr) has been used with success.⁴²⁰

There are two major reactions of organocuprates as a carbon nucleophile:⁴²¹ (*1*) reaction with alkyl halides and (*2*) conjugate addition with α , β -unsaturated ketones. With α , β -unsaturated ketones, conjugate addition is promoted when ether is used as a solvent.⁴¹⁸ The substitution reaction is promoted by the use of THF or ether-HMPA as a solvent.⁴¹⁸ As mentioned earlier, the mechanism of these reactions probably involves a one-electron transfer, although other mechanistic proposals are in the literature.⁴²² The general reactivity of organocuprates with electrophiles follows the order:⁴¹⁸

$$\underset{R}{\overset{O}{\coprod}} \sim R-CHO > R-OTs \approx \underset{R}{\overset{O}{\longleftarrow}} > R-I > R-Br > R-Cl > \underset{R}{\overset{O}{\coprod}} \sim R-CO_2R^1 > R-C\equiv N \gg R^{-C}$$

^{416.} Gilman, H.; Jones, R.G.; Woods, L.A. J. Org. Chem. 1952, 17, 1630.

^{417.} For an extensive discussion of the mechanism of reaction between organocuprates and alkyl haldies or epoxides, see Mori, S.; Nakamura, E.; Morokuma, K. J. Am. Chem. Soc. 2000, 122, 7294.

^{418.} Posner, G.H. An Introduction to Synthesis Using Organocopper Reagents, Wiley, New York, 1980.

^{419.} Whitesides, G.M.; Fischer, Jr., W.F.; San Filippo, Jr., J.; Bashe, R.W.; House, H.O. *J. Am. Chem. Soc.* **1969**, *91*, 4871.

^{420.} House, H.O.; Wilkins, J.M. J. Org. Chem. 1978, 43, 2443.

^{421. (}a) Ashby, E.C.; DePriest, R.N.; Tuncay, A.; Srivastava, S. *Tetrahedron Lett.* 1982, 23, 5251; (b) Posner, G.H.; Ting, J.-S.; Lentz, C.M. *Tetrahedron* 1976, 32, 2281; (c) Johnson, C.R.; Dutra, G.A. J. Amer. Chem. Soc. 1973, 95, 7777, 7783; (d) Smith, R.A.J.; Hannah, D.J. *Tetrahedron* 1979, 35, 1183; (e) Castro, C.E.; Havlin, R.; Honwad, V.K.; Malte, A.; Mojé, S. J. Am. Chem. Soc. 1969, 91, 6464; (f) House, H.O.; Koespell, D.G.; Campbell, W.J. J. Org. Chem. 1972, 37, 1003.

^{422.} Nakamura, E.; Mori, S. Angew. Chem. Int. Ed. 2000, 39, 3750.

The R groups can be primary, secondary, tertiary alkyl, aryl, or heteroaryl and can bear remote functionality such as ethers, acetals or ketals, sulfides, or other labile groups.⁴¹⁸

8.7.A.ii. Coupling Reactions. In previous sections, Grignard reagents and organolithium reagents usually gave poor yields of coupling products in a reaction with an alkyl halide unless catalyzed by transition metals. Cuprous salts were used with Grignard reagents to catalyze coupling reactions (sec. 8.4.B.i). Addition of cuprous salts to organolithium reagents gave organocuprates (R'₂CuLi), the active species in the coupling reaction, and this has become the

$$R - X + R^{1}_{2}CuLi \xrightarrow{\text{ether}} R - R^{1}$$

preferred method for the formation of coupled products (R–R') from alkyl halides.⁴²³ The reactivity of the cuprate is due in large part to the low ionic character of the Cu–C bond; the low oxidation potential (0.15 eV) separating Cu(I) and Cu(II) ions, the tendency for Cu to form polynuclear Cu clusters, and the formation of mixed-valence Cu compounds.⁴¹⁸ The coupling reacation of organocuprates with alkyl halides, tosylates or acetates is straightforward, but the mechanistic details have been a source of some controversy. Primary alkyl halides generally give good yields of the coupling product (R–R¹) in a Wurtz-type process⁴²⁴ (sec. 8.5.B.ii). Table 8.18⁴¹⁹ shows the relative reactivity of di-*n*-butylcuprate with various organohalides to give the alkane R–R'. The reaction proceeded faster and in higher yield in THF than in ether. From this study the order of reactivity of the halide substrate was determined to be RI > RBr > RCl. The secondary halide gave reduced yields, and tertiary halides gave virtually no reaction under conditions that produced large amounts of product from primary halides. Sulfonate esters such as mesylates or tosylates and also acetates are susceptible to displacement by organocuprates.⁴²⁵

$R-X + n-Bu_2CuLi \xrightarrow{ether, -20^{\circ}C} R-n-Bu$					
<u>R-X</u>	Solvent	<u>Time (h)</u>	<u>% R–<i>n</i>-Bu</u>		
1-Iodopentane	ether ether THF	$\begin{array}{c}1\\26\\1\end{array}$	68 70 98		
1-Bromopentane	THF	1	98		
1-Chloropentane	THF ether ether	1 1 26	80 10 10		
2-Bromopentane	THF THF	$\frac{1}{26}$	12 12		
2-Bromo-2-methylpentane	THF	1	<10		
[Reprinted with permission from Whitesides, G.M.; Fischer Jr., W.F.; San Filippo Jr., J.; Bashe, R.W.; House, H.O. J. Am. Chem. Soc. 1969 , 91, 4871. Copyright © 1969 American Chemical Society.]					

 Table 8.18. Relative Reactivity of Lithium Di-n-butyl Cuprate with Alkyl Halides

^{423.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, **1999**, pp 118-122.

^{424.} House, H.O. Acc. Chem. Res. 1976, 9, 59.

^{425. (}a) Posner, G.H.; Ting, J.S.; Lentz, C.M. *Tetrahedron* 1976, 32, 2281; (b) Posner, G.H.; Ting, J.S. *Tetrahedron Lett.* 1974, 683.

The coupling reaction is extremely useful for joining alkyl fragments or alkyl-aryl, aryl-aryl, or heteroaryl fragments by reaction with alkyl halides or sulfonate esters.⁴²⁶ In a typical synthetic application, the cuprate derived from **418** (via Li–Br exchange with *tert*-butyllithium and reaction with Li_2CuCl_4 to form the aryl cuprate) reacted with the allylic bromide shown to give a 74% yield of **419** in the Overman and co-workers synthesis of the kinesin motor protein inhibitor adociasulfate 1.⁴²⁷ Note that organocuprates react with secondary bromides with inversion whereas the identical reaction with a secondary iodide proceeds with racemization. In this synthesis, TBDMS is *tert*-butyldimethylsilyl (see sec. 7.3.A.i).



If there is excessive steric encumbrance when an organocuprates reacts with an allylic system, the coupling may proceed by a S_N2' like pathway (sec. 2.6.A.iii).⁴²⁸ A synthetic example is taken from a synthesis of paroxetine (PAXIL) by Krische and Koech in which allylic phosphonate **420** reacted with the cuprate derived from ClSiMe₂(O*i*-Pr) to give the S_N2' product **421** in 96% yield.⁴²⁹ Cyclopropylcarbinyl halides react with organocuprates⁴³⁰ such as di-*n*-butylcuprate to give the (*E*)-homoallylic compound.



In addition to the expected displacement of alkyl halides, organocuprates react with vinyl halides and aryl halides to give good yields of the coupled product.⁴³¹ This alkenyl halide coupling reaction proceeds with high stereoselectivity, in contrast to the Grignard and organolithium coupling reactions. (*E*)-2-Bromostyrene (**422**) reacted with diphenylcuprate to give a 90:<2 mixture of (*E/Z*) stilbenes (**423/424**).⁴²⁴ Similarly, the (*Z*)-bromide (**425**) gave a <1:73 mixture of **423/424**.⁴²⁴ It is apparent that the coupling proceeded with little or no loss of stereochemical

- 427. Bogenstätter, M.; Limberg, A.; Overman, L.E.; Tomasi, A.L. J. Am. Chem. Soc. 1999, 121, 12206.
- 428. (a) Magid, R.M. *Tetrahedron* 1980, 36, 1901; (b) DeWolfe, R.H.; Young, W. Chem. Rev. 1956, 56, 753; (c) Goering, H.L.; Singleton, Jr, V.D. J. Org. Chem. 1983, 48, 1531.
- 429. Koech, P.K.; Krische, M.J. Tetrahedron 2006, 62, 10594.
- 430. (a) Hrubiec, R.T.; Smith, M.B. *Tetrahedron* 1984, 40, 1457; (b) Hrubiec, R.T.; Smith, M.B. J. Org. Chem. 1984, 49, 385.
- 431. (a) Bowlus, S.B.; Katzenellenbogen, J.A. J. Org. Chem. 1973, 38, 2733; (b) Cooke, Jr., M.P. Tetrahedron Lett. 1973, 1983.

^{426.} Kojima, Y.; Wakita, S.; Kato, N. Tetrahedron Lett. 1979, 4577.

integrity of the vinyl bromide. Vinyl sulfonate esters such a triflate derivatives [triflate = $OTf = -SO_2CF_3$] also react with organocuprates to give the coupling product.⁴³² A mechanism of "oxidative" addition between a cuprate and an alkenyl halide has been proposed.⁴³³ The initially formed π -complex is thought to behave as a cuprio(III)cyclopropane⁴³⁴ rather than a simple CuI/alkenyl halide complex, where charge transfer takes place from the 3*d* orbital of the bent R₂Cu moiety to the π^*/σ^* -mixed orbital of a deformed alkenyl halide. Subsequent C–Br bond cleavage in this complex may go through the "three-centered" or the "eliminative" pathway, of which the latter is preferred.



Coupling reactions with alkyl halides often use a large excess of cuprate as mentioned above, which can be a severe limitation if the halide precursor to the organocuprate is difficult to prepare or unavailable from commercial sources. A solution is to prepare a cuprate with a ligand that is less reactive, allowing selective transfer of the substituent of choice. An example is the use of **428** in a reaction with **429** that gave **430**, an intermediate in Corey and co-worker's synthesis of *N*-methylmaytansine.^{435,381} The alkynyl-copper bond in species such as **428** is very stable relative to alkyl-copper and alkenyl-copper bonds. When an alkyl-alkynyl cuprate or an alkenyl-alkynyl cuprate is prepared, the alkyl or alkenyl group will be transferred selectively. Cuprate **428** was prepared by reaction of the Cu(I) species **426** with vinyl bromide **427** in the presence of *n*-butyllithium.⁴³⁵ It is noteworthy that only the alkenyl group was transferred to the benzylic iodide, and not the alkynyl moiety. In general, this method allows a synthetically prepared halide such as **427**, which may be difficult to obtain in pure form, to be coupled to another halide with greater efficiency.

$$Me \xrightarrow{Me}_{Me} Cu + Br_{Me} \xrightarrow{OTHP} OTHP \xrightarrow{n-C_4H_9Li, THF} Me \xrightarrow{OMe}_{Me} Cu Li^+ Cu Li^+ Me \xrightarrow{Me}_{Me} OTHP$$

^{432.} Corey, E.J.; Das, J. J. Am. Chem. Soc. 1982, 104, 5551.

^{433.} Yoshikai, N.; Nakamura, E. J. Am. Chem. Soc. 2004, 126, 12264.

^{434.} Mori, S.; Nakamura, E.; Morokuma, K. Organometallics 2004, 23, 1081.

^{435. (}a) Corey, E.J.; Wetter, H.F.; Kozikowski, A.P.; Rao, A.V.R. *Tetrahedron Lett.* 1977, 777; (b) Corey, E.J.; Bock, M.G.; Kozikowski, A.P.; Rao, A.V.R.; Floyd, D.; Lipshutz, B. *Ibid.* 1978, 1051.



The alkyl or aryl halide -organocuprate coupling disconnection is

$$R-R^{1} \swarrow R-X+R^{1}-X \quad Ar-R \swarrow Ar-X+R-X \quad R \swarrow R \swarrow R-X+\frac{X}{R} \bigcap R \bigcap R R \stackrel{V}{\longrightarrow} R-X \stackrel{V}{\longrightarrow} R$$

8.7.A.iii. Reaction with Epoxides. Organocuprates also react with epoxides, ⁴³⁶ with addition occurring at the less sterically hindered carbon, typical of a nucleophilic addition. In the Toyota and co-worker's synthesis of (+)-mycalamide A, dimethylcuprate reacted with epoxide 431 to give 432 in >90% yield.⁴³⁷ The ring opening was highly selective for the alcohol shown.



The epoxide-organocuprate disconnection is

$$\begin{array}{c} HO \\ \searrow \\ R \end{array} \overset{R^1}{\longrightarrow} \begin{array}{c} R^{1} - X + \underset{R}{\overset{O}{\longrightarrow}} \begin{array}{c} & \bigcirc \\ & & & \\ \end{array} \end{array}$$

8.7.A.iv. Reaction with Acid Chlorides. As briefly mentioned in Section 8.4.C.ii, the reaction of a dialkyl cuprate and an acid chloride is an excellent method for the synthesis of ketones.^{438,439} The reaction usually requires low temperatures to isolate the ketone product^{425,424} and is more general than the use of a dialkylcadmium reagent (sec. 8.4.C.ii). Masamune et al. used this reaction to convert acid **433** to ketone **434** in a synthesis of erythronolide.⁴⁴⁰ In this case, oxalyl

438. Fex, T.; Froborg, J.; Magnusson, G.; Thorén, S. J. Org. Chem. 1976, 41, 3518.

^{436. (}a) Herr, R.W.; Wieland, D.M.; Johnson, C.R. J. Am. Chem. Soc. 1970, 92, 3813; (b) Staroscik, J.; Rickborn, B. Ibid. 1971, 93, 3046; (c) Wieland, D.M.; Johnson, C.R. Ibid. 1971, 93, 3047; (d) Anderson, R.J. Ibid. 1970, 92, 4978; (e) Herr, R.W.; Johnson, C.R. Ibid. 1970, 92, 4979; (e) Anderson, R.J.; Adams, K.G.; Chinn, H.R.; Henrick, C.P. J. Org. Chem. 1980, 45, 2229.

^{437.} Kagawa, N.; Ihara, M.; Toyota, M. J. Org. Chem. 2006, 71, 6796.

^{439.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, **1999**, pp 1389-1400.

^{440. (}a) Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. J. Am. Chem. Soc. 1981, 103, 1566; (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk.A.; Garvey, D.S. Ibid. 1981, 103, 1568.

chloride was used to prepare the requisite acid chloride.



The acid chloride-organocuprate disconnection is

$\overset{O}{\nearrow}_{R^1} \sqsubset$	° R [⊥] OH	+	R ¹ -X
---	------------------------	---	-------------------

8.7.A.v. Reaction with Aldehydes and Ketones.⁴⁴¹ The reaction of organocuprates with aldehydes is fast. Dimethylcuprate reacted with benzaldehyde to give phenylethyl alcohol at $< -90^{\circ}$ C. Ketones react more slowly, as illustrated by the reaction of dimethylcuprate and 5-nonanone which occurred at about -10° C to give 5-methyl-5-nonanol.⁴⁴² No reaction occurred at lower temperatures. Higher temperatures are often required for reaction of hindered aldehydes, leading to significant decomposition of the organocuprate via disproportionation before the addition reaction occurs. Still showed a typical cuprate addition to an aldehyde when dimethylcuprate reacted with **435** (at -78° C) to give **436**.⁴⁴³ In this case the excellent



diastereoselectivity (30:1 anti:syn 436) was the result of chelation control (secs. 4.7.B, sec. 6.2.E). The cuprate addition usually follows Cram's rule (sec. 4.7.B), in the absence of chelation effects. Di-*n*-butylcuprate reacted with 437 in the presence of chlorotrimethylsilane to give a 6.4:1 mixture of 438/439 (439 is predicted by Cram's

rule, the Cram product).⁴⁴⁴ As mentioned above, ketones react very slowly with cuprates. Addition of chlorotrimethylsilane to the reaction can alleviate this problem (this was used in the reaction of **437**). With conjugated ketones, addition of chlorotrimethylsilane enhances the rate of 1,2-addition. It also enhances Cram diastereoselectivity when an organocuprate reacts with a chiral aldehyde.⁴⁴⁴ There is a clear enhancement of rate, and this is probably not just a consequence of trapping the enolate anion that results from conjugate addition. The precise mechanism is unclear but may be related to an equilibration reaction for organocuprate conjugate additions.⁴⁴³

^{441.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 1150-1151.

^{442.} Posner, G.H.; Whitter, C.E.; McFarland, P.E. J. Am. Chem. Soc. 1972, 94, 5106.

^{443.} Still, W.C.; McDonald III, J.H. Tetrahedron Lett. 1980, 21, 1031.

^{444.} Matsuzawa, S.; Isaka, M.; Nakamura, E.; Kuwajima, I. *Tetrahedron Lett.* **1989**, *30*, 1975 and references cited therein.

$$\begin{array}{c} Ph \\ Me \end{array} \xrightarrow{} CHO \xrightarrow{2 n-Bu_2CuLi, THF} \\ \textbf{Me} \xrightarrow{} Me_3SiCl, -70^{\circ}C \end{array} \xrightarrow{Ph} \xrightarrow{OTMS} \\ \textbf{Me} \xrightarrow{} n-C_4H_9 \end{array} + \begin{array}{c} Ph \\ Me \end{array} \xrightarrow{} OTMS \\ \textbf{Me} \xrightarrow{} n-C_4H_9 \end{array}$$

8.7.A.vi. Conjugate Addition. Organocuprates react with α,β-unsaturated conjugated aldehyde and ketone derivatives such as **440** to give almost exclusive 1,4-addition.⁴⁴⁵ Initial conjugate addition generates an enolate anion (**441**, secs. 9.2.A, 9.7.A), and subsequent hydrolysis gives ketone **442**. The reaction is believed to proceed via reductive elimination of a σ-allylcopper(III) compound that leads to a C–C bond.⁴⁴⁶ A density functional study has shown that the C–C bond formation occurs directly from the π-allyl complex via an enyl[$\sigma + \pi$]-type transition state.⁴⁴⁷ A synthetic example is taken from Ollivier, Piras and co-worker's synthesis of grandisol, inwhich conjugated aldehyde **444** (prepared from conjugated ester **443**) reacted with lithium dimethylcuprate to give a 97% yield of **445**.⁴⁴⁸ In addition to the dialkyllithium cuprates, it is also possible to form magnesium cuprates that react in an identical manner. A synthetic example is taken from Harris and Padwa's synthesis of 6-epi-indolizidine 223A,⁴⁴⁹ in which conjugated piperidone **446** reacted with diethylmagnesium cuprate to give **447** in 90% yield.



After the initial addition of a cuprate to a conjugated system, an enolate anion is formed, which can react in a subsequent reaction with an alkyl halide, an aldehyde or another electrophilic species. In a synthesis of *dendrobatid* alkaloid 251F by Aubé and co-worker's,⁴⁵⁰

^{445.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 1599-1613

^{446.} See (a) Goering, H. L.; Singleton Jr., V. D. J. Org. Chem. 1983, 48, 1531; (b) Goering, H. L.; Tseng, C. C. J. Org. Chem. 1983, 48, 3986; (c) Goering, H. L.; Kantner, S. S. J. Org. Chem. 1984, 49, 422.

^{447.} Yamanaka,, M.; Kato, S.; Eiichi Nakamura, E. J. Am. Chem. Soc. 2004, 126, 6287.

^{448.} Bernard, A.M.; Frongia, A.; Ollivier, J.; Piras, P.P.; Secci, F.; Spiga, M. Tetrahedron 2007, 63, 4968.

^{449.} Harris, J.M.; Padwa, A. J. Org. Chem. 2003, 68, 4371.

^{450.} Wrobleski, A.; Sahasrabudhe, K.; Aubé, J. J. Am. Chem. Soc. 2002, 124, 9974.

conjugate addition of dimethyl cuprate to α , β -unsaturated ketone **448** gave enolate anion **449**. Subsequent addition of the aldehydes shown gave **450**, after elimination of water to form the conjugated ketone unit. The ability to add two alkyl substituents via conjugate addition and then alkylation with an alkyl halide or another electrophile (a double alkylation) is an important variation of conjugate addition with organocuprates. In general, the two groups incorporated by such a double-alkylation have a trans relationship,⁴⁵¹ but the cis-trans ratio varies with the organocuprate and the substrate.



The reaction is not limited to the use of simple organocuprates. Mixed cuprate **428** was one example. Another example that used an unsymmetrical organocuprate is Sih and co-worker's reaction of (–)-dialkenylcuprate (**451**) with **452** to give **453**, an intermediate in a prostanoid synthesis.^{452,453} As with all Michael-type additions, the reaction of organocuprates is somewhat sensitive to steric effects at the reactive π bond. Addition usually occurs to the less sterically hindered position. Steric hindrance also plays a role in the diastereoselectivity of the reaction. Heathcock et al. showed that the position of the substituent relative to conjugated system is a significant factor in the formation of (*E*) or (*Z*) isomers from cycloheptenones.⁴⁵⁴ The stereoselectivity increases as the group on the ring increases in size and when it is closer to the β-carbon.



Because of the reactivity of aldehydes with cuprates (sec. 8.7.A.v), 1,2-addition to α , β -unsaturated aldehydes can compete with 1,4-addition, although the former usually predominates. α , β -Unsaturated ketones normally give 1,4-addition. In Table 8.19,⁴⁵⁵ Marshall showed how the copper reagent and the proportion of RLi to Cu influenced the ratio of 1,2- to 1,4-addition with **454** and di(4-pentenyl)cuprate. Reaction with this cuprate gave the 1,2-addition product **455**, the 1,4-addition products **456** and **457**, and the dialkylation product **458** when the initial

^{451.} Paczkowski, R.; Maichle-Mössmer, C.; Maier, M.E. Org. Lett. 2000, 2, 3967.

^{452. (}a) Sih, C.J.; Salomon, R.G.; Price, P.; Peruzzoti, G.; Sood, R. J. Chem. Soc. Chem. Commun. 1972, 240;
(b) Sih, C.J.; Salomon, R.G.; Price, P.; Sood, R.; Peruzzotti, G. J. Am. Chem. Soc. 1975, 97, 857.

^{453.} Kluge, A.F.; Untch, K.G.; Fried, J.H. J. Am. Chem. Soc. 1972, 94, 9256.

^{454.} Heathcock, C.H.; Germroth, T.C.; Graham, S.L. J. Org. Chem. 1979, 44, 4481.

^{455.} Marshall, J.A.; Audia, J.E.; Shearer, B.G. J. Org. Chem. 1986, 51, 1730.

addition product was quenched with iodomethane. Diminishing the RLi/Cu ratio to <2:1 suppressed 1,2-addition. The best yields were obtained when the intermediate enolate was trapped with chlorotrimethylsilane, which was mentioned above with the reaction of **437** with di-*n*-butylcuprate. The improvement in yield is presumably due to rate acceleration.^{456,457} The enhanced diastereoselectivity can be seen in the addition of divinylcuprate to **459**, which gave two racemic silyl enol ethers, **460** and **461**. In the absence of chlorotrimethylsilane the ratio of enolates was 56:44 (this is also the diastereomeric ratio of **460/461**, although the silyl enol ether cannot be formed without addition of chlorotrimethylsilane).which also increased the product ratio to >99:1 (**460/461**).⁴⁵⁷ Isolation of the silyl enol ethers was followed by hydrolysis to give **462** as the major product.

Table 8.19. Organolithium/Cuprous Halide Ratio in 1,2 versus 1,4-Addition of
Organocuprates to 454

$\begin{array}{c} \overset{\text{OTBS}}{\overbrace{}} \\ \overset{\text{H}}{\overbrace{}} \\ \overset{\text{H}}{\overbrace{}} \\ \overset{\text{H}}{\overbrace{}} \\ \overset{\text{CuLi}}{2. E^{+}} \\ \textbf{454} \\ \end{array} $	OTBS H . H . H + , (, (55 4	OTBS H .	H CHO 457	$\frac{1}{1} + \frac{1}{1}$	OTBS H . e CHO 458
Conditions	$\underline{\mathbf{E}}^+$	<u>% 455</u>	<u>% 456</u>	<u>% 457</u>	<u>% 458</u>
2 RLi, CuI, Me ₂ S, 2:1 ether:THF, 14h	MeI	17	37	19	7
2 RLi, CuBr•SMe ₂ , 2:1 ether:THF, 14h	MeI	17 ^a	20	16	8
1.8 RLi, CuI, Me ₂ S, 1.6:1 ether:THF, 14	h MeI	0	30	22	33
1.8 RLi, CuI, Me ₂ S, 1.8:1 ether:THF, 10	h H ₃ O ⁺	0	65		
1.6 RLi, CuI, Me ₂ S, 1.6:1 ether:THF, 14	h H ₃ O ⁺	0^{b}	0		
1.8 RLi, CuI, Me ₂ S, 1.6:1 ether:THF, 14	h 1. TSCl 2. H ₃ O ⁺	0	91		
^a + 10% of 454 . ^b + 92% of 454 .					
[Reprinted with permission from Marshall, J.A Copyright © 1986 American Chemical Society	; Audia, J.E.; Sheard	er, B.G. J. Or	g. Chem. 1986	<i>51</i> , <i>1</i> 730.	



Conjugated esters are less reactive than the corresponding ketones.⁴⁵⁸ Conjugate addition to ester **463** gave only 8% methylated product **464** after reaction with dimethylcuprate for 44 hours.

458. (a) Posner, G.H. Organic. React. 1972, 19, 1; (b) Normant, J.F.; Synthesis 1972, 63.

^{456.} Taylor, R.J.K. Synthesis 1985, 364.

 ^{457. (}a) Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* 1985, 26, 6015, 6019; (b) Alexakis, A.; Berlan, J.; Besace, Y. *Ibid.* 1986, 27, 1047; (c) Johnson, C.R.; Marren, T.J. *Ibid.* 1987, 28, 27.

Despite the steric hindrance of the hexyl group, the analogous ketone (**465**) gave a quantitative yield of **466** under the same conditions. Although conjugated esters usually react slower than conjugated ketones, they do give conjugate addition products unless a more reactive group is present in the molecule. Addition of the diallylcuprate shown to ester **467**, for example, gave the alkylated ester (**468**) an intermediate in Nicolaou and co-worker's synthesis of tylosin.⁴⁵⁹ Note that conjugated esters show greatly enhanced reactivity when RCu•BF₃ is used as the organocopper reagent.⁴⁶⁰ With highly hindered systems, especially β , β -disubstituted conjugate esters, RCu•BF₃ is the reagent of choice.⁴⁶¹



The disconnection for cuprate conjugate addition is

$$O = \bigwedge_{R}^{R^{1}} \bigcap_{R} O = \bigwedge_{R}^{R} R + R^{1} - X$$

8.7.A.vii. Asymmetric Induction. Addition of an organocuprate to a conjugated system often creates a new stereogenic center, so a discussion of diastereoselectivity and possible enantioselectivity is appropriate. Controlling asymmetric induction in organocuprate addition reactions involves the use of organocuprates whose chirality has been modified.⁴⁶² Typical chiral groups include 1,2,5,6-di-*O*-isopropylidene- α -*D*-glucofuranose (469), (*S*)-proline (470), (*S*)-*N*-methylproline (471), and neomenthyl thiol (472).⁴⁶² Addition of the organocuprate to cyclohexenone in the presence of these chiral ligands gave the chiral ketone, 473, but with generally poor %ee (4.7-26% ee).⁴⁶²

461. Yamamoto, Y.; Maruyama, K. J. Am. Chem. Soc. 1978, 100, 3240.

^{459.} Nicolaou, K.C.; Pavia, M.R.; Seitz, S.P. J. Am. Chem. Soc. 1982, 104, 2027, 2030.

 ^{460. (}a) Yamamoto, Y. Angew. Chem. Int. Ed. 1986, 25, 947; (b) Lipshutz, B.H.; Ellsworth, E.L.; Siahaan, T.J. J. Am. Chem. Soc. 1988, 110, 4834; (c) Idem, Ibid. 1989, 111, 1351.

^{462.} Tomioka, K.; Koga, K. in *Asymmetric Synthesis, Vol. 2*, Morrison, J.D. (Ed.), Academic Press, New York, *1983*, pp 219-221.



In acyclic systems, Mukaiyama and co-workers found that addition of chiral magnesium cuprate $R(Z^*)$ CuLi derived from 471 gave good asymmetric induction.⁴⁶³ Lithium cuprates derived



netric induction.⁴⁶³ Lithium cuprates derived from **474**, however, gave poor yields and modest % ee.⁴⁶⁴ Kretchmer⁴⁶⁵ also used the alkaloid (–)-sparteine (**163**) as a complexing agent with magnesium cuprates (RCuMgX₂), but observed < 10% optical purity upon addition to α , β -unsaturated ketones. Langer

and Seebach observed products with up to 27% optical purity when the co-solvent for the reaction was (*R*,*R*) or (*S*,*S*)-1,4-(dimethylamino)-2,3-dimethoxybutane.⁴⁶⁶ Gustafsson used an asymmetric ligand (RR*CuLi) where $R^* = (-)-[1-(dimethylamino)-ethyl]$ phenyl⁴⁶⁷ or *o*-[cyclohexyl(dimethylamino)methyl]-phenyl,⁴⁶⁸ but they gave < 5% ee in organocuprate reactions.

Bertz and co-workers showed that cuprates added to cyclohexenone to give the 3-phenyl derivative (**475**) in optical yields of 0-50%.⁴⁶⁹ Typical examples are R¹R²N = (4*S*,5*S*)-(+)-5-amino 2,2-dimethyl-4-phenyl-1,3-dioxane (the reaction proceeded in 62%



yield, 50% ee); (R) or (S) α -methylbenzylamine (70% yield, 30% ee); (*R*) or (*S*) α -(1-naphthyl) ethylamine (70% yield, 30% ee); and (-) α -2-naphthylethyl-amine (50% yield, 40% ee).⁴⁶⁹

Good-to-excellent asymmetric induction has been achieved with a new generation of chiral additives or chiral ligands.⁴⁷⁰ Corey et al. achieved enantioselectivities in the 75-95% range with the chiral controller ligand **476**, obtained from (+) or (–)-ephedrine.⁴⁷¹ This chiral ligand

^{463.} Imamoto, T.; Mukaiyama, T. Chem. Lett. 1980, 45.

^{464.} Huché, M.; Berlan, J.; Pourcelot, G.; Cresson, P. Tetrahedron Lett. 1981, 1329.

^{465.} Kretchmer, R.A. J. Org. Chem. 1972, 37, 2744.

^{466.} Langer, W.; Seebach, D. Helv. Chim. Acta 1979, 62, 1710.

^{467.} Gustafsson, B.; Nilson, M.; Ullenius, C. Acta Chem. Scand. Ser. B 1977, B31, 667.

^{468.} Gustafsson, B. Tetrahedron 1978, 34, 3023.

^{469.} Bertz, S.; Dabbagh, G.; Sundararajan, G. J. Org. Chem. 1986, 51, 4953.

^{470.} For a review of enantioselective conjugate additions see Sibi, M.P.; Manyem, S. Tetrahedron 2000, 56, 8033.

^{471.} Corey, E.J.; Naef, R.; Hannon, F.J. J. Am. Chem. Soc. 1986, 108, 7114.

was converted to the asymmetric copper complex (477), and reaction with cyclohexenone with selective transfer of the butyl group gave 3-butylcyclohexanone (478) in 80% yield (80% ee).⁴⁷¹ Similar reaction with ethyllithium gave the ethyl derivative in 66% yield with an optical purity > 95% ee. If the organolithium reagent was heavily contaminated with alkoxides, however, the optical purity was as low as 9% ee.



A different approach to solving this problem is to attach a chiral auxiliary to the enone substrate. An auxiliary is a chiral material that is attached to an achiral substrate. The asymmetry of the auxiliary controls the selectivity of the reaction and is then removed in a separate chemical step. Posner and co-workers studied the use of optically pure α -carbonyl- α , β -ethylenic sulfoxides (**479**, see sec. 3.9.A.ii for the preparation of optically active sulfoxides).⁴⁷² Conjugate addition of di-(2,2,-dimethylpropyl)magnesium cuprate and then reductive cleavage of the C–S bond of the sulfoxide with aluminum amalgam gave 3-(2,2-dimethylpropyl)cyclohexanone (**480**) in 99% yield as a 7:1 (*R/S*) mixture.⁴⁷² Oppolzer and Löher prepared (–)-(8*E*)-phenylmenthyl acrylates such as **481**.⁴⁷³ The conformational stability of the cyclohexyl ring in **481** ensured that the phenyl group blocked one face of the α , β -unsaturated ester, leading to excellent facial selectivity during the addition. Conjugate addition (here with phenylcopper-boron trifluoride-see the previous discussion in sec. 8.7.A.vi) followed by saponification of the ester (**482** was formed in 76% yield) gave the acid **483** in > 99% ee. Oppolzer et al. also reported excellent diastereoselectivity for addition of organocopper derivatives to α , β -unsaturated sulfonamides derived from camptor (see sec. 11.9.A for further discussion of chiral auxiliaries).⁴⁷⁴



^{472.} Posner, G.H.; Frye, L.L.; Hulce, M. Tetrahedron 1984, 40, 1401.

^{473.} Oppolzer, W.; Löher, H.J. Helv. Chim. Acta 1981, 64, 2808.

 ^{474. (}a) Oppolzer, W.; Mills, R.J.; Pachinger, W.; Stevenson, T. *Helv. Chim. Acta* 1986, 69, 1542; (b) Oppolzer, W.; Schneider, P. *Ibid.* 1986, 69, 1817.



Other asymmetric substrates can be used with organocuprates. One example is Scolastico and co-worker's report that reaction of **484** with di-*n*-butylcuprate gave a 70% yield of **485** (78-98 % ee).⁴⁷⁵ Using this auxiliary, alkylated ester **485** was converted to aldehyde **486** in 80% yield with 91% asymmetric induction.⁴⁷⁵



487

70% yield (82% ee).476

8.7.B. Higher Order Cuprates

Cuprates are very useful but there are a few problems associated with them, including reactivity and thermal stability. In an attempt to circumvent these problems, Lipshutz and co-workers developed the so-called *higher order mixed cuprates* (R₂Cu(CN)Li₂),⁴⁷⁷ prepared by reaction of two equivalents of organolithium reagent with cuprous cyanide (CuCN).⁴⁷⁸ Mixed cuprates

2 R—Li + CuCN \longrightarrow R₂Cu(CN)Li₂

react faster than Gilman reagents with alkyl halides, even secondary halides. Mixed cuprates are generally the reagent of choice for this purpose. Table 8.20^{479a} shows the reaction of alkyl

^{475.} Bernardi, A.; Cardani, S.; Poli, G.; Scolastico, C. J. Org. Chem. 1986, 51, 5041.

^{476.} Malmberg, H.; Nilsson, M.; Ullenius, C. Tetrahedron Lett. 1982, 23, 3823.

^{477.} Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. Tetrahedron 1984, 40, 5005.

^{478.} Lipshutz, B.H.; Wilhelm, R.S. J. Am. Chem. Soc. 1982, 104, 4696.

^{479. (}a) Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A.; Parker, D. J. Org. Chem. 1984, 49, 3928; (b) Yamamoto, K.; Iijima, M.; Ogimura, Y.; Tsuji, J. Tetrahedron Lett. 1984, 25, 2813; (c) Takahashi, T.; Okumoto, H.; Tsuji, J. Ibid. 1984, 25, 1925.

halides with the higher order cuprate derived from butyllithium and cuprous cyanide to give the alkane, R-*n*-Bu. Note that Bertz questioned the validity of structure of cuprates such as R₂Cu(CN)Li₂, citing ¹³C NMR evidence that the reagent actually existed as R₂CuLi•LiCN in THF.⁴⁸⁰ Lipshutz contradicted this conclusion,⁴⁸¹ when the ¹H and ¹³C NMR spectra of the higher order cuprate Me₂Cu(CN)Li₂ were compared with those of Me₂CuLi•LiBr and Me₂CuLi•LiI, and he concluded that the spectra were not at all similar. Lipshutz concluded that the spectra proved the presence of a Cu–CN bond, and a higher order cuprate structure. *Ab initio* evidence,^{482a} additional NMR evidence⁴⁸³ as well as kinetic evidence^{482b,c} by Bertz again called these structures into question, and he suggested their structure to be cyano-Gilman reagents. Several studies concluded there is no higher order cuprate, but that the active species is best described as R₂CuLi•LiCN.^{482d} A theoretical study suggests that a minor species R(CN)CuLi•LiR may play an important role due to its greatly enhanced reactivity.⁴⁸⁴

$R-X + 2 n-Bu_2Cu(CN)Li_2 \longrightarrow R-n-Bu$				
<u>Halide</u>	<u>Temp. (°C)</u>	<u>Time (h)</u>	<u>% R–n-Bu</u>	
Iodocyclopentane	-78	2	82	
Bromocyclopentane	0	6	86	
Iodocyclohexane	-78	1	100	
Bromocyclohexane	25	6	41	
2-Iodopentane	-50	2	99	
2-Bromopentane	0→25	2	94	
2-Chloropentane	25	11	28	
2-Tosyloctane	25	8	>80	
(10 equivalents cuprate)				
[Reprinted with permission from Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A.; Parker, D. J. Org. Chem. 1984, 49, 3928. Copyright © 1984 American Chemical Society.]				

Table 8.20.	Reaction of Higher	Order Cyanocuprates	with Alkyl Halides
	0	v i	e e

Higher order organocuprates react with chiral halides to give chiral coupling products. When (*R*)-2-bromooctane (**489**) reacted with the mixed-cuprate [EtMeCu(CN)Li₂], a 72% yield of (*R*)-3-methylnonane (**490**) was obtained,^{479b,c} which is the result expected of a nucleophilic $S_N 2$



like displacement of the bromide. As mentioned in Section 8.7.A, the reaction probably proceeds via single electron-transfer process, but the

stereochemistry of this reaction mimics nucleophilic substitution. The extent of inversion is very dependent on the nature of the reacted organocuprate, however. 2-Iododecane derivatives

484. Nakamura, E.; Yoshikai, N. Bull. Chem. Soc. Jpn. 2004, 77, 1.

^{480.} Bertz, S.H. J. Am. Chem. Soc. 1990, 112, 4031.

^{481.} Lipshutz, B.H.; Sharma, S.; Ellsworth, E.L. J. Am. Chem. Soc. 1990, 112, 4032.

⁽a) Snyder, J.P.; Spangler, D.P.; Behling, J.R.; Rossiter, B.E. J. Org. Chem. 1994, 59, 2665; (b) Snyder, J.P.; Bertz, S.H. J. Org. Chem. 1995, 60, 4312; (c) Bertz, S.H.; Miao, G.; Eriksson, M. Chem. Commun. 1996, 815. Also see (d) Krasuse, Angew. Chem. Int. Ed. 1999, 38, 79.

^{483.} Bertz, S.H.; Nilsson, K.; Davidsson, Ö.; Snyder, J.P. Angew. Chem. Int. Ed. 1998, 37, 314.

showed virtually no inversion of configuration when with Gilman-type reagent or with higher order cuprates.^{479a} Bromides, on the other hand, gave virtually complete inversion with both reagents.^{479a} The smallest amount of inversion was obtained with symmetrical cuprates, and the largest amount with mixed cuprates.

This displacement reaction is not limited to allyl derivatives or to substrates a bearing halide leaving group. Both vinyl and aryl derivatives react with higher order cuprates, similar to the Gilman reagents. Lipshutz and Elworthy found that vinyl triflates are particularly useful in cuprate coupling reactions. The reaction of vinyl triflate **491** reacted with the mixed cuprate **492**, gave **493** in 87% yield.⁴⁸⁵ An interesting feature of cuprate **492** is the presence of 2-thienyl as an unreactive ligand (see **428**). Lipshutz et al. found this to be most effective for the selective transfer of the group other than thienyl.⁴⁸⁶ This is analogous to the use of alkynyl groups as unreactive substituents in Gilman reagents. The mixed-alkyl cuprates are easily prepared by sequential addition of two different organolithium reagents to cuprous cyanide. In general, for reagents such as R(Me)Cu(CN)Li₂ (R > Me), the R group is transferred selectively for both the halide displacement and the conjugate addition.



Epoxide ring opening is more efficient with the higher order cuprate than with Gilman reagents, and attack is at the less sterically hindered carbon.^{479a} Reaction of **494** with di-*n*-propylcuprate, for example, gave only 15-30% of **495**. Similar reaction with $Pr_2Cu(CN)Li_2$ gave an 86% yield of **495**.^{487,488} Higher order cuprates give excellent yields of conjugate addition with α , β -unsaturated compounds, as do Gilman reagents.⁴⁸⁹ In the Reddy and co-worker's synthesis of (+)-cyanthiwigin AC,⁴⁹⁰ conjugated ketone **496** reacted with the higher order methyl cuprate derived from 2-propenyllithium and CuCN to give an 85% yield of **497**.



^{485.} Lipshutz, B.H.; Elworthy, T.R. J. Org. Chem. 1990, 55, 1695.

^{486.} Lipshutz, B.H.; Kozlowski, J.A.; Parker, D.A.; Nguyen, S.L.; McCarthy, K.E. J. Organomet. Chem. 1985, 285, 437.

^{487.} Lipshutz, B.H.; Kozlowski, J.; Wilhelm, R.S. J. Am. Chem. Soc. 1982, 104, 2305.

^{488.} Lipshutz, B.H.; Kotsuki, H.; Lew, W. Tetrahedron Lett. 1986, 27, 4825.

^{489.} Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. J. Org. Chem. 1984, 49, 3938.

^{490.} Reddy, T.J.; Bordeau, G.; Timble, L. Org. Lett. 2006, 8, 5585.


Dieter et al. developed an α -aminoalkylcuprate that allows incorporation of nitrogen. Cyanocuprate **498** reacted with cyclohexenone in the presence of chlorotrimethylsilane to give a 98% yield of the conjugate addition product **499**.^{491a}



The disconnections for the higher order cuprate are identical to those observed with Gilman reagents.

8.8. YLIDS

Ylids are defined as compounds in which a carbanionic carbon is immediately adjacent to an atom bearing a positive center. Many atoms can support a positive charge but phosphorus, sulfur or nitrogen lead to particularly useful and interesting compounds. This section will deal with ylids and their reactions, focusing on phosphorus ylids such as **500**, sulfur ylids



such as **501** or nitrogen ylids such as **502**. Of these three R^{+}_{N-C-} classes of ylids,⁴⁹² the phosphonium ylids (**500**) and other R^{-}_{502} phosphorus ylids are the most studied due to their relative stability and ability to generate alkenes from carbonyl compounds. The sulfur ylids (**501**) are also well known,⁴⁹³

and react as carbanions with carbonyl derivatives to give oxiranes or cyclopropane derivatives. The nitrogen ylids (**502**) are not as well known as isolable entities, but there are a few synthetic applications when stabilizing groups are present.⁴⁹⁴

8.8.A. Phosphorus Ylids

8.8.A.i. Wittig Reagents. Phosphorus ylids have a history dating to the 1890s and to the

^{491. (}a) Dieter, R.K.; Alexander, C.W.; Nice, L.E. *Tetrahedron* 2000, 56, 2767. Also see (b) Dieter, R.K.; Lu, K.; Velu, S.E. J. Org. Chem. 2000, 65, 8715.

^{492.} Johnson, A.W. Ylid Chemistry, Academic Press, New York, 1966

^{493.} Trost, B.M.; Melvin, Jr., L.S. Sulfur Ylides, Academic Press, New York, 1975.

^{494.} Zugravescu, I.; Petrovanu, M. Nitrogen-Ylid Chemistry, McGraw Hill, New York, 1976.

pioneering work of Michaelis and Gimborn.⁴⁹⁵ Wittig and co-workers found that phosphonium salts (**503**) were generated by an $S_N 2$ reaction of a trialkylphosphine with an alkyl halide, and they reacted with strong bases to give the corresponding ylid (**504**), a resonance stabilized species.^{496a} The discovery of these phosphorus ylids may have been serendipitous, because Wittig was attempting to make pentavalent phosphorus compounds.

$$PPh_3 \xrightarrow{\text{Me-I}} Ph_3^+ \xrightarrow{\text{Ph}_3P} Me \quad \overline{I} \xrightarrow{\text{base}} \left[Ph_3^+ \xrightarrow{\text{Ph}_3P} H_2 \xrightarrow{\text{CH}_2} Ph_3P = CH_2\right]$$

In earlier work, Staudinger and Hauser found that phosphazines ($R_3P=N-N=CR_2$) generated $R_3P=CR_2$ upon heating and they examined some of the chemistry of these phosphorus ylids,⁴⁹⁷ but Wittig discovered that they reacted with aldehydes and ketones to form an alkene product. This latter reaction has come to be called the **Wittig olefination reaction**, or simply the **Wittig reaction**.⁴⁹⁶ In early papers, it was postulated that initial reaction of ylid **504** with a ketone or aldehyde generated a labile intermediate called a betaine **505**, which collapsed to an oxaphosphetane (**506**). Either of these intermediates can decompose to give an alkene (reaction of **504** with benzophenone, for example, led to 1,1-diphenylethene, **384**), and a trisubstituted phosphine oxide (in the case of **504**, triphenylphosphine).⁴⁹⁶ The P–O bond is particularly strong, with a bond dissociation energy of 130-140 kcal mol⁻¹ (544.2-586.0 kJ mol⁻¹).⁴⁹⁸ Formation of this strong bond is largely responsible for decomposition of the intermediate betaine or oxaphosphetane to give the alkene.

$$\begin{array}{c} Ph_{3}P \xrightarrow{+} CH_{2} \xrightarrow{Ph} Ph \xrightarrow{O} \left[\begin{array}{c} Ph_{3}P \xrightarrow{+} O \\ & \swarrow Ph \end{array} \right] \xrightarrow{+} \left[\begin{array}{c} Ph_{3}P \xrightarrow{+} O \\ & \swarrow Ph \end{array} \right] \xrightarrow{+} \left[\begin{array}{c} Ph_{3}P \xrightarrow{+} O \\ & \swarrow Ph \end{array} \right] \xrightarrow{-} Ph_{3}P=O \xrightarrow{Ph} Ph \xrightarrow{Ph} Ph \xrightarrow{O} Ph \xrightarrow{Ph} Ph \xrightarrow{$$

Betaine or oxaphosphetane intermediates are not usually isolable, although an oxaphosphetane derived from a highly specialized ylid was isolated as a stable solid, and its structure was determined by X-ray crystallography.⁴⁹⁹ The existence of betaine derivatives as discrete intermediates has been called into question, and this issue will be addressed in connection with mechanistic discussions of the Wittig reaction in section 8.8.A.ii.

Examination of the generalized structure 508 (generated from phosphonium salt 507) shows

^{495.} Michaelis, A.; Gimborn, H.V. Berichte 1894, 27, 272.

^{496. (}a) Wittig, G.; Rieber, M. Annalen 1949, 562, 187; (b) Wittig, G.; Geissler, G. Ibid. 1953, 580, 44; (c) Wittig, G.; Schöllkopf, U.; Chem. Ber. 1954, 87, 1318; (d) Gensler, W.J. Chem. Rev. 1957, 57, 191 (see p 218); (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-101; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 696-697.

^{497. (}a) Stauadinger, H.; Hauser, E. Helv. Chim. Acta 1921, 4, 861; (b) Staudinger, H.; Meyer, J. Ibid. 1919, 2, 612.

^{498.} Hartley, S.B.; Holmes, W.S.; Jacques, J.K.; Mole, M.F.; McCoubrey, J.C. Quart. Rev. Chem. Soc. 1963, 17, 204.

^{499.} Bestmann, H.J.; Roth, K.; Wilhelm, E.; Böhme, R.; Burzlaff, H. Angew. Chem. Int. Ed. 1979, 18, 876.

the formal charge on phosphorus is +1. When R¹ and/or R² are alkyl, the positive charge on phosphorus is diminished due to the inductive effect of the alkyl groups. Such ylids are more reactive with a ketone or aldehyde, but decomposition of the resulting oxaphosphetane is more difficult. The R groups on the phosphorus should not be a group that contains α -protons, since deprotonation would lead to a mixture of isomeric ylids. Reaction of **509** with *n*-butyllithium, for example, gives two ylids, **510** and **511**. To prevent this problem, all but one of the R groups should *not* possess α -hydrogens, which accounts for the use of Ph₃P and other triaryl phosphines in the Wittig reaction. If R¹ in **507** is electron-withdrawing (COR, CO₂R, CN, etc.), the negative charge of the ylid is delocalized by that group, decreasing both the nucleophilicity and reactivity of the carbanionic carbon. Such ylids usually react well with aldehydes, but ketones are less reactive.



The strength of the base required for deprotonation of the phosphonium salt to form the ylid depends on the relative acidity of the α proton, which depends on the alkyl or aryl group attached to that carbon (-CHR¹R² in **508**) as well as the nature of the groups attached to the phosphorus. The α -hydrogen of a phosphonium salt such as **507** is much more acidic than that of the

analogous structure without the phosphorus atom (2,2-dimethylpropane). The pK_a for H_a of fluorene (**201**), for example, is 25^{500} but H_a in the triphenylphosphonium derivative **512** has a pK_a of <10.⁵⁰¹ The proton (H_a) in the



corresponding ammonium salt (**513**) has a p K_a slightly less than that of fluorene.⁵⁰² Electronreleasing groups such as alkyl (R¹ = R² = alkyl in **507**) make the α -hydrogen less acidic, whereas the presence of electron-withdrawing groups (R¹ and/or R² = COR, CO₂R, CN, etc. in **507**) make that hydrogen more acidic. The wide range of acidity for hydrogens in phosphonium salts leads to a range of different bases that can be used. Both sodium hydride and potassium hydride have been used as bases, as has dimsyl sodium (sodium salt of DMSO) in DMSO. It is more common to use *n*-butyllithium, *tert*-butyllithium or *sec*-butyllithium in ether or THF. Guanidine bases also promote the Wittig reaction, as well as the Horner-Wadsworth-Emmons reaction discussed in section 8.8.A.ii, under mild conditions, with high efficiency and isolation of products is facile.⁵⁰³ Guanidine bases include 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD,

^{500.} McEwen, W.K. J. Am. Chem. Soc. 1936, 58, 1124.

^{501.} Johnson, A. Wm.; LeCount, R.B. Tetrahedron 1960, 9, 130.

^{502.} Wittig, G.; Felletschin, G. Annalen 1944, 555, 133.

^{503.} Simoni, D.; Rossi, M.; Rondanin, R.; Mazzali, A.; Baruchello, R.; Malagutti, C.; Roberti, M.; Invidiata, F.P. Org. Lett. 2000, 2, 3765.



514) and its methyl derivative MTBD(**515**), which were ≈ 100 times more effective than tetramethyl guanidine (TMG, **516**). It is also noted that Wittig reactions can be done using stable phosphorus ylids in the presence of silica gel in hexane.⁵⁰⁴

Triarylphosphonium ylids⁵⁰⁵ react with aldehydes and ketones by what is known as the **Wittig reaction**,^{496c,506} to form alkenes. The reaction is particularly useful for incorporating exocyclic methylene groups.^{507,508} For this and other work, Wittig was awarded the Nobel prize in 1979. Poor stereocontrol is sometimes a problem in Wittig olefination reactions (see sec. 8.8.A.ii).⁵⁰⁹ The synthetic applications are generally straightforward. In Crimmins and co-worker's

synthesis of astrogorgin,⁵¹⁰ ketone **517** reacted with triphenylphosphonium ylid $Ph_3P=C(Me)CO_2Et$ to give a near quantitative yield of **518**. A variety of substituents (R¹ and R² in **508**) can be attached to the carbanionic carbon in



phosphorus ylids.⁵¹¹ Arylalkyl ylids (Ph₃P=CRAr) are commonly used in synthesis. Even reactive groups such as esters and nitriles can be used. Other functionality is compatible with this reaction. The functionalized phosphonium salt **519** reacted with the NaH and THF, and was then treated with thiophene-aldehyde **520** to give a 55% yield of **521** in Al-Mourabit and co-worker's synthesis of haliclamine A.⁵¹² Otherwise reactive functional groups such as aldehydes, ketones, esters, etc. can be incorporated into the ylid. In a synthesis of perophoramidine by Weinreb and Artman, the lactone unit of ylid **522** was successfully incorporated in **523** in 98% yield.⁵¹³ In general, an ylid that contains an electron-withdrawing group at the carbanionic carbon is less reactive, but they still react with carbonyl derivatives. The phosphorane can even possess another acidic proton, although two equivalents of base are required to generate the anion ylid. An example is Ph₃P(CH₂)₃CO₂H, which was converted first to the carboxylate

510. Crimmins, M.T.; Brown, B.H.; Plake, H.R. J. Am. Chem. Soc. 2006, 128, 137.

^{504.} Patil, V.J.; Mävers, U. Tetrahedron Lett. 1996, 37, 1281.

^{505.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 327-332.

^{506. (}a) Wittig, G.; Haag, W. Berichte 1955, 88, 1654; (b) Wittig, G. Acc. Chem. Res. 1974, 7, 6; (c) Schöllkopf, U. Angew. Chem. 1959, 71, 260; (d) Trippett, S. Quart. Rev. Chem. Soc. 1963, 17, 406;

^{507. (}a) Corey, E.J.; Mitra, R.B.; Uda, H. J. Am. Chem. Soc. 1963, 85, 362; (b) Idem Ibid. 1964, 86, 485.

^{508.} Ley, S.V.; Murray, P.J. J. Chem. Soc. Chem. Commun. 1982, 1252.

^{509.} For a computational study of reactivity and selectivity in the Wittig reaction, see Robiette, R.; Richardson, J.; Aggarwal, V.K.; Harvey, J.N. J. Am. Chem. Soc. 2006, 128, 2394.

^{511.} Reference 492, pp 119-129.

^{512.} Michelliza, S.; Al-Mourabit, A.; Gateau-Olesker, A.; Marazano, C. J. Org. Chem. 2002, 67, 6474.

^{513.} Artman III, G.D.; Weinreb, S.M. Org. Lett. 2003, 5, 1523.

anion, and then to the ylid by treatment with base.⁵¹⁴ The resulting ylid reacted with aldehydes in the usual manner to give an alkene, but several carbons should separate the anionic centers. Protected alcohols can also be incorporated as part of the ylid.⁵¹⁴ It is even possible to do the Wittig reaction in aqueous media with water-soluble phosphonium salts developed by Warren and co-workers.⁵¹⁵ There are other nonclassical applications of the Wittig reaction,⁵¹⁶ and intramolecular versions are known.⁵¹⁷



Incorporation of electron rich groups other than alkyl on the ylid is also possible. A useful application of this idea is the chain extension of ketones or aldehydes. In the synthesis of (+)-N_a-methylsarpagine,⁵¹⁸ Cook and co-worker's treated ketone **524** with a methoxymethyl ylid to generate a vinyl ether product (**525**). Subsequent acid hydrolysis converted the vinyl ether to aldehyde **526** in 90% overall yield. This sequence converted a ketone to an aldehyde with a one-carbon chain extension. Vinyl sulfides can also be formed by Wittig methodology (see **375** and **378** in sec. 8.6.B.ii).⁵¹⁹



The presence of halogen atoms in a molecule is compatible with formation of an ylid and subsequent Wittig reaction. Carbon tetrabromide and triphenylphosphine have been used to give vinyl dibromide products, which are rapidly converted to the corresponding alkyne. Indeed, this is an important synthetic route to alkynes called the **Corey-Fuchs procedure**

^{514.} Marinier, A.; Deslongchamps, P. Tetrahedron Lett. 1988, 29, 6215.

^{515.} Russell, M.G.; Warren, S. J. Chem. Soc. Perkin Trans. 1 2000, 505.

^{516.} Murphy, P.J.; Lee, S.E. J. Chem. Soc. Perkin Trans. 1 1999, 3049.

^{517.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, p 328.

^{518.} Zhao, S.; Liao, X.; Cook, J.M. Org. Lett. 2002, 4, 687.

^{519.} Corey, E.J.; Carpino, P. J. Am. Chem. Soc. 1989, 111, 5472.

previously mentioned in chapter 2.⁵²⁰ Double elimination is possible to generate an alkyne. The reaction of **527** with this reagent gave vinyl dibromide **528** in 88% yield, as part of Ellman and co-worker's synthesis of (+)-lithospermic acid.⁵²¹ When **528** was treated with an excess of butyllithium and then methyl chloroformate, alkyne **529** was isolated in 93%% yield.

$$MeO \xrightarrow{H} O \xrightarrow{H$$

For use in the Wittig reaction, it is important that the R¹ and R² groups on the ylid (see **508**) not be subject to spontaneous fragmentation when the carbanion is formed. This is illustrated by bis(phosphonium) salt **530**, which upon treatment with phenyllithium did not give the ylid but rather decomposed to triphenylphosphine and the vinyl phosphonium salt **531**.⁵²² Such fragmentation occurs most often when a leaving group is β to the phosphorus atom. Conversion to the bis(ylid) is straightforward when the two phosphorus-containing groups are separated by three or more methylene groups.⁵²²

$$\stackrel{+}{Ph_{3}P} \xrightarrow{P}_{PPh_{3}} \stackrel{PhLi}{\longrightarrow} PPh_{3} + \stackrel{+}{\swarrow} \stackrel{P}{PPh_{3}}$$
530
531

Ylids with a heteroatom substituent can decompose to a carbene intermediate (sec. 13.9.B). Butoxymethyl ylid **532** spontaneously fragmented to triphenylphosphine and carbene **533**, for example. This carbene reacted with an additional molecule of the ylid (**527**) to give the1,2-dienolether **535** via the zwitterion **534**.⁵²³

$$\begin{array}{c} Ph_{3}P^{+} & - & - & PPh_{3} \\ \hline & & \\ \mathbf{532} & \mathbf{533} & \mathbf{533} \end{array} \xrightarrow{} \begin{array}{c} - & PPh_{3} \\ BuO & \mathbf{534} & OBu \end{array} \xrightarrow{} \begin{array}{c} - & PPh_{3} \\ \hline & & \mathbf{535} & \mathbf{535} \end{array} \xrightarrow{} OBu \\ \hline & & \mathbf{535} & OBu \end{array}$$

Phosphorus ylids rarely rearrange, but the presence of a reactive group such as a halide⁵²⁴ or ester⁵²⁵ can lead to anomalous products. In one example, the carbanionic carbon of **536** displaced the bromide to give triphenylcyclobutylphosphonium bromide (**537**), via an internal $S_N 2$ reaction.⁵²² In ester **538**, nucleophilic attack of the carbanionic carbon generated α -keto ylid **539** via acyl substitution.⁵²³

^{520.} Corey, E.J.; Fuchs, P.L. Tetrahedron Lett. 1972, 3769.

^{521.} O'Malley, S.J.; Tan, K.L.; Watzke, A.; Bergman, R.G.; Ellman, J.A. J. Am. Chem. Soc. 2005, 127, 13496.

^{522. (}a) Wittig, G.; Eggers, H.; Duffner, P. Annalen 1958, 619, 10; (b) Trippett, S. Chem. & Ind. (London) 1956, 80; (c) Dicker, D.W.; Whiting, M.C. J. Chem. Soc. 1958, 1994.

^{523. (}a) Wittig, G.; Böll, W. Chem. Ber. 1962, 95, 2526; (b) Trippett, S. Proc. Chem. Soc. 1963, 19.

^{524. (}a) Mondon, A. Annalen 1957, 603, 115; (b) Scherer, K.V.; Lunt III, R.S. J. Org. Chem. 1965, 30, 3215.

^{525.} Bergel'son, L.D.; Vaver, V.A.; Barsukov, L.I.; Shemyakin, M. Izvest. Akad. Nauk. SSSR 1963, 1134.



8.8.A.ii. (*E*/*Z*) **Isomers in Wittig Reactions.** When a phosphorus ylid reacts with an aldehyde or ketone, the alkene that is formed is a mixture of (*E*) and (*Z*) isomers.⁵²⁶ Initial postulations suggested that the stereochemistry of the alkene products was controlled by the stereochemistry of the betaine, which rapidly collapsed to an oxaphosphetane. Subsequent fragmentation to the alkene occurred via syn-elimination.⁴⁹² An example of this postulate is shown by the reaction of ylid **540** and 2-butanone to generate betaine **541**, and the anti-oxaphosphetane, **543**.⁴⁹² Syn elimination led to the (*E*)-alkene, **545**. The reaction mixture also contained betaine **542**, the precursor to the syn oxaphosphetane (**544**), which led to the (*Z*) alkene, **546**.



Resonance stabilized ylids such as Ph₃P=CHCO₂Et and Ph₃P=CHPh give predominantly the (E) alkene, whereas non-stabilized vlids such as $Ph_3P=CHEt$ give predominantly the (Z) alkene.⁵²⁷ These results are also rationalized in terms of a betaine intermediate. For resonancestabilized ylids, formation of the betaine is reversible and equilibration favors formation of the thermodynamically more stable anti-betaine. The anti-betaine may also collapse faster than the syn-betaine.⁵²⁸ If elimination of triphenylphosphine oxide is slow, the possibility of equilibration to the anti-betaine is maximized, and there will be increased amounts of the (E) alkene. Tricyclohexylphosphine ylids are less electrophilic than triphenyl ylids, and they show greater selectivity for formation of the (E) alkene.⁵²⁹ Addition of a protic solvent or a Lewis acid to coordinate the oxygen atom of the betaine leads to more (Z) isomer.^{526,529} If the metal coordinates with the betaine (or the oxaphosphetane) after reaction of an aldehyde and Ph₃P=CHCO₂Me, this coordination slows down the interconversion of **549** and **550** and diminishes the stereoselectivity. The equilibrium concentration of 547 and 548 is not the same as the concentration of **549** and **550**. The complexed form shows some preference for the anticonformation 550, which gives a slight preference for the (Z) isomer. These arguments refer only to stabilized phosphoranes and ignore the stereochemistry of the groups around the phosphorus

^{526.} Reucroft, J.; Sammes, P.G. Quart. Rev. Chem. Soc. 1971, 25, 135.

^{527.} Schlosser, M.; Christman, K.F. Annalen 1967, 708, 1.

^{528.} Speziale, A.J.; Bissing, D.E. J. Am. Chem. Soc. 1963, 85, 1888, 3878.

^{529.} Bestmann, H.J.; Kratzer, O. Berichte 1962, 95, 1894.

atom, which are stable throughout the reaction.⁵³⁰ When the ylid is not stabilized (as when it possesses alkyl substituents), betaine and oxaphosphetane formation is essentially irreversible. Reaction of unsaturated ylids with aromatic aldehydes or α , β -unsaturated aldehydes shows some reversibility, however.⁵³¹ Lithium salts are usually present in the reaction medium, and this can lead to poor yields of alkene products. Under salt free conditions, the reaction appears to be under kinetic control, leading to the syn-betaine and the (*Z*) alkene.⁵³²



Schlosser et al. found that manipulating the solvent and the salt concentration allows some control of the (E/Z) selectivity, and rationalized his observations in terms of a betaine intermediate.⁵³³ Betaine **551** can react with unreacted *n*-butyllithium to form a dilithio species (**552**), which rapidly establishes an equilibrium with **553**.⁵³³ If lithium salts are added to this equilibrium, oxaphosphetane formation and elimination from the kinetic syn betaine **551** is inhibited. Further addition of excess butyllithium leads to **552** and **553**. This equilibrium favors the anti species **553**. Protonation leads to betaine **555** (or the potassium salt, **554**) and thereby to an oxaphosphetane which collapses to the anti alkene. This study suggests that excess base and excess salt promotes equilibration and formation of the anti (E) alkene.



To obtain the (Z) alkene, salt free conditions are required. The syn betaine is relatively hindered, and as the carbonyl reactant becomes more hindered there is a greater preference for the (Z)

^{530.} Bladé-Font, A.; McEwen, W.; VanderWerf, C.A. J. Am. Chem. Soc. 1960, 82, 2646, 2396.

^{531.} Schlosser, M.; Christmann, K.F. Angew. Chem. Int. Ed. 1965, 4, 689; Ibid. 1964, 3, 636.

^{532. (}a) Bestmann, H.J. Angew. Chem. Int. Ed. 1965, 4, 583; (b) Wittig, G.; Eggers, H.; Duffner, P. Annalen 1958, 619, 10.

^{533. (}a) Schlosser, M.; Müller, G.; Christmann, K.F. Angew. Chem. Int. Ed. 1966, 5, 667; (b) Schlosser, M.; Christmann, K.F. Ibid. 1966, 5, 126.

alkene.⁵³⁴ Schneider explained this effect by considering the importance of the substituent configuration around the phosphorus atom during reaction.⁵³⁵ The intermediate **556** (apical oxygen and equatorial ylid carbon) must rotate at the O-C bond to form the betaine (**557** or **558**). The Ph \leftrightarrow R² steric interaction is maintained throughout, but the R¹ \leftrightarrow Ph interaction in **556** inhibits formation of **558** and favors **557** (the syn betaine), leading to the (*Z*) alkene. With protic solvents or polar additives, the configuration of the phosphorane may change, and this model does not apply. For stabilized ylids, the pre-betaine intermediate is represented by **559** and is oriented so that the positive end is attracted to the nucleophilic acyl carbon, and forms the anti betaine and the (*E*) alkene.⁵²⁹ The R¹ group rotates to form the betaine, and this rotation minimizes the R¹ \leftrightarrow CO₂Et interaction.



The intermediacy of the betaines in the Wittig reaction has been questioned, and Vedejs has proposed an alternative explanation. The Wittig reaction is subject to solvent effects that indicate a nonpolar transition state for stabilized ylids.⁵³⁶ There appears to be no direct evidence for the presence of betaines, and none have been isolated. Alternatively, Vedejs and Snoble detected oxaphosphetanes as the only observable intermediates in several Wittig reactions of non-stabilized ylids,⁵³⁷ using ³¹P NMR.⁵³⁸ Vedejs devised a test for the betaine mechanism based on changes in phosphorus stereochemistry of betaines versus oxaphosphetanes.⁵³⁹ The results of this test suggested that "the conventional betaine mechanism^{540,505e} can play at most a minor role in the Wittig reaction".⁵³⁹ Vedejs points out that the "stereochemical test does not necessarily disprove mechanisms via intermediates with lifetimes that are short compared to the time scale of bond rotation."⁵³⁹



Vedejs proposes two oxaphosphetane models to predict the stereochemistry in the Wittig reaction. For systems that give primarily cis alkenes, a cisoxaphosphetane is required based on the assumption that the reaction proceeds by an early transition

- 534. Axen, U.; Lincoln, F.H.; Thompson, J.L. J. Chem. Soc. Chem. Commun. 1969, 303.
- 535. Schneider, W.P. J. Chem. Soc. Chem. Commun. 1969, 785.
- 536. (a) Frøyen, P. Acta Chem. Scand. 1972, 26, 2163; (b) Aksnes, G.; Khalil, F.Y. Phosphorus 1972, 2, 105 [Chem. Abstr. 78:70865v 1973]; (c) Idem, Ibid. 1973, 3, 79 [Chem. Abstr. 79:145749s 1973].
- 537. Vedejs, E.; Snoble, K.A.J. J. Am. Chem. Soc. 1973, 95, 5778.
- 538. Vedejs, E.; Meier, G.P.; Snoble, K.A.J. J. Am. Chem. Soc. 1981, 103, 2823.
- 539. Vedejs, E.; Marth, C.F. J. Am. Chem. Soc. 1990, 112, 3905.
- 540. (a) Maercker, A. Org. React. 1965, 14, 270; (b) Schlosser, M. Topics Stereochem. 1973, 5, 1.

state (like starting materials), and the oxaphosphetane has a puckered conformation (**560**).⁵⁴¹ Similarly, for systems that give trans-alkenes as the major product, a *trans*-oxaphosphetane is required, the reaction is assumed to proceed by a late transition state (product-like) and the oxaphosphetane has a planar structure (**561**).

A trans-oxaphosphetane is more stable than the cis-oxaphosphetane, and equilibrium conditions favors the trans-product. Kinetic control conditions appear to dominate Wittig reactions and lead to the cis-product using this analogy.⁵³⁷ Vedejs and co-workers suggest that there is no single, dominant Wittig transition state geometry but rather a continuum of related mechanistic variants.⁵³⁸ Examination of **560** and **561** suggests that the interplay of 1,2-steric interactions (interactions of substituents on P and C2 in **560** and also on C2-C3) and 1,3-steric interactions (interactions of substituents on P and C3 in **561**) will determine cis or trans selectivity.⁵³⁹ Puckered transition states are more important when large groups at the α -carbon provide increasing 1,3-steric interactions. For stabilized ylids, 1,2-interactions dominate the transition state, leading to trans selectivity.

Maryanoff et al. also studied this problem, and found a prevalence of (*Z*)-alkene and cisoxaphosphetane in the salt-free Wittig reaction, which forms the alkene by syn elimination of Ph₃P=O.⁵⁴² His work also suggests a very slow equilibration of cis- and trans-oxaphosphetanes relative to the rate of alkene formation. There is a significant concentration dependence on the stereochemistry of the reaction. Increasing concentration favored the trans-oxaphosphetane.⁵⁴² At high dilution, alkenes were generally formed with (*Z*)-selectivity in THF with LiBr present. The concentration effect may be associated with sequestration of lithium by THF. The ability of lithium soluble salts to promote formation of (*E*)-alkenes from non-stabilized ylids is well known (see above), but it is concentration dependent in THF. Based on studies with many types of phosphorus ylids, Maryanoff et al. concluded that betaines may have a "meaningful, albeit transient, existence,⁵⁴²" despite the lack of direct evidence for their existence. Since kinetic experiments demonstrated that cis-oxaphosphetanes undergo reversal to the ylid and an aldehyde faster than does the trans-oxaphosphetane (see above), the degree of stereochemical drift in Wittig reactions is probably due to the relative rates of oxaphosphetane reversal.

Stereochemical control in a Wittig reaction is seen in Wu and co-worker's synthesis of annonacin,⁵⁴³ in which aldehyde **562** was treated with ylid **563** to give an 81% yield of **564**. Pan and co-worker's⁵⁴⁴ synthesis of (–)-6,7-dehydroferruginyl methyl ether is a trans specific reaction, in contrast to formation of **564**. Aldehyde **565** reacted with the ylid generated from phosphonium chloride **566** to give the trans alkene (**567**) in 60% yield.

^{541.} Vedejs, E.; Marth, C.F. J. Am. Chem. Soc. 1988, 110, 3948.

^{542. (}a) Maryanoff, B.E.; Reitz, A.B.; Mutter, M.S.; Inners, R.R.; Almond, Jr., H.R.; Whittle, R.R.; Olofson, R.A. J. Am. Chem. Soc. 1986, 108, 7664; (b) Maryanoff, B.E.; Reitz, A.B.; Duhl-Emswiler, B.A. Ibid. 1985, 107, 217.

^{543.} Hu, T.-S.; Wu, Y.-L.; Wu, Y. Org. Lett. 2000, 2, 887.

^{544.} Gan, Y.; Li, A.; Pan, X.; Chan, A.S.C.; Yang, T.-K. Tetrahedron: Asymmetry 2000, 11, 781.



8.8.A.iii. Phosphine Oxides and Phosphonate Esters.⁵⁴⁵ Many extensions of the Wittig reaction have been introduced that improve or modify the reactivity and/or stereoselectivity of the ylid. Horner et al. showed that α -lithiophosphine oxides such as that derived from **568** react with aldehydes or ketones to give a β -hydroxy phosphine oxide (**569**) as an isolable species.⁵⁴⁶ Subsequent treatment with base liberates the alkene (**570**). Wadsworth and Emmons modified the Horner reaction to use phosphonate ester derivatives such as **571**. Reaction with aldehydes or ketones (such as benzaldehyde) in the presence of base gave the olefination product **572** in 84% yield.⁵⁴⁷ These variations have come to be called the Horner-Wadsworth-Emmons olefination.⁵⁴⁸ It is sometimes called Horner-Emmons olefination.



The major product of olefination with phosphonate carbanions is usually the (*E*)-isomer.⁵⁴⁹ However, a (*Z*)-selective reaction has been developed that uses sodium iodide and DBU as the base.⁵⁵⁰ Speziale and Ratts suggested that increased amounts of (*Z*) alkene were obtained by increasing the steric bulk of the L and L¹ groups in **573** and **576**, formed by reaction of the phosphonate ester ylid with a carbonyl compound. This equilibrium favors the anti

^{545.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 332-335.

^{546.} Horner, L.; Hoffmann, H.; Wippel, J.H.G.; Klahre, G. Berichte 1959, 92, 2499.

^{547.} Wadsworth, Jr, W.S.; Emmons, W.D. J. Am. Chem. Soc. 1961, 83, 1733.

^{548. (}a) Boutagy, J.; Thomas, R. Chem. Rev. 1974, 74, 87; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 334-335.

^{549.} Wadsworth, D.H.; Schupp III, O.E.; Seus, E.J.; Ford, Jr., J.A. J. Org. Chem. 1965, 30, 680.

^{550.} Ando, K.; Oishi, T.; Hirama, M.; Ohno, H.; Ibuka, T. J. Org. Chem. 2000, 65, 4745.

conformation 573 over 576, and elimination gives more (*Z*) product, 575.⁵⁵¹ This model assumes that steric encumbrance is more important in 573 and 576 than in oxaphosphetanes 574 and 577, respectively, that are required for syn elimination to the alkene. This equilibrium generally favors 575 over 578 due to the stereochemical preferences in the initially formed ylid products.



Bases such as *n*-butyllithium, potassium *tert*-butoxide or sodium hydride are usually required to generate the phosphonate carbanion.⁵⁵² The nucleophilicity of that anion is influenced by the nature of the metal ion. Addition of a metal ligand to the reaction mixture also influences the relative ease of removal of the α -proton. With some metals, a weaker base can be used to generate the carbanion.⁵⁵³ Addition of metal salts to **579** (R = Et) led to formation of carbanion **580**, which was stabilized by chelation to the metal.⁵⁵⁴ Addition of complexing Lewis acids such as LiBr or MgBr₂ allowed the ylid to be formed with a base as weak as triethylamine. Magnesium bromide was the most efficient metal additive for producing this product.⁵⁵⁴ Subsequent reactions were done with cyclohexanone to give **581** (also with benzaldehyde to give the =CHPh derivative), and the best results were obtained in ether solvents or acetonitrile with lithium halides, although magnesium bromide was also effective.



Still and Gennari⁵⁵⁵ showed that octanal reacted with the carbanion derived from **579** to give a mixture of **582** and **583**. Using KN(TMS)₂ (potassium hexamethyldisilazide) as a base (sec. 9.2.B) in THF in the presence of 18-crown-6, gave an 8:1 mixture of **582/583** in 81% yield when OR = OMe in **579**. Changing OR to OCH₂CF₃ led to isolation of a 12:1 mixture of **582/583** in 90% yield.⁵⁵⁵ Reaction of **579** (R = CH₂CF₃) with benzaldehyde, under the

^{551.} Speziale, A.J.; Ratts, K.W.O. J. Am. Chem. Soc. 1963, 85, 2790.

^{552.} Wadsworth, Jr., W.S. Org. React. 1977, 25, 73.

^{553. (}a) Bottin-Strzalko, T.; Corset, J.; Froment, F.; Ponet, M.J.; Seyden- Penne, J; Simmonin, M.J. J. Org. Chem. 1980, 45, 1270; (b) Blanchette, M.A.; Choy, W.; Davies, J.T.; Essenfeld, A.P.; Masamune, S.; Roush, W.R.; Sakai, T. Tetrahedron Lett. 1984, 25, 2183.

^{554.} Rathke, M.W.; Nowak, M. J. Org. Chem. 1985, 50, 2624.

^{555.} Still, W.C.; Gennari, C. Tetrahedron Lett. 1983, 24, 4405.

same conditions, gave a >50:1 mixture of (*Z*/*E*) alkenes in >95% yield.⁵⁵⁵ When Triton B (PhCH₂NMe₃⁺OH⁻) was used in THF with **579** (R = CH₂CF₃) a 7:1 mixture of **582/583** was obtained (84%), but the use of KO*t*-Bu in THF gave a 2:5 mixture of **582/583** in 70% yield.⁵⁵⁵ These studies show that the preference for the (*Z*)-alkene product is strongly influenced by the reaction conditions and phosphonate carbanion chosen for the reaction. An asymmetric olefination using a benzopyranoisoxazolidine auxiliary was reported, generating alkylidene cyclohexane derivatives with good asymmetric induction.⁵⁵⁶

$$n-C_{6}H_{13}$$
 CHO $\frac{base}{579}$ $n-C_{6}H_{13}$ CO₂Me + $n-C_{6}H_{13}$ CO₂Me + $cO_{2}Me$ + $cO_{2}Me$

There are many applications of phosphonate ester methodology in organic synthesis. In a synthesis of (+)-himgaline,⁵⁵⁷ Evans and Adams reacted phosphonate ester **585** with aldehyde **584** in the presence of Hünig's base and lithium perchlorate to incorporate the chiral auxiliary for an 82%% yield of conjugated carbonyl **586**.



Intramolecular olefination reactions are possible using phosphonate carbanions. This type of cyclization is also possible with Wittig reagents, but it is more facile with the more stable phosphonate carbanions. An example is taken from a synthesis of palmerolide A by De Brabender and co-worker's, in which **587** was cyclized to macrolide **588** containing the conjugate ketone moiety in 70% yield from the primary alcohol precursor to **587**.⁵⁵⁸



Warren showed that olefination of ketones and aldehydes, or even esters with phosphine oxide carbanions, allowed some control of stereochemistry in the alkene products. Reaction with

^{556.} Abiko, A.; Masamune, S. Tetrahedron Lett. 1996, 37, 1077.

^{557.} Evans, D.A.; Adams, D.J. J. Am. Chem. Soc. 2007, 129, 1048.

^{558.} Jiang, X.; Liu, B.; Lebreton, S.; De Brabander, J.K. J. Am. Chem. Soc. 2007, 129, 6386

an aldehyde or ketone generates diastereomeric β -hydroxyphosphine oxide products, which can be isolated and then chromatographically separated. Reaction of 589 with *n*-butyllithium was followed by addition of 3,4-methylenedioxybenzaldehyde (590, known as piperonal) to give a 9:1 mixture of **591/592**, the syn and anti alcohol, respectively.⁵⁵⁹ The pure syn alcohol 591 was isolated in 75% yield by chromatography on silica gel. Subsequent treatment with sodium hydride in DMF gave the (Z)-alkene, α -isosafrole (593). If 589 reacted first with *n*-butyllithium and then with the analogous ester (594), the keto-phosphine oxide 595 was produced. Reduction of the ketone with sodium borohydride gave predominantly ($\approx 6:1$) the anti isomer 596, which gave the (E)-alkene 597 upon reaction with sodium hydride. An interesting application of this methodology is to extend the chain of an aldehyde by one carbon (R-CHO \rightarrow RCH₂CHO).⁵⁶⁰ Indeed, many functional groups can be incorporated into the phosphonate ester, including nitriles, esters, carboxylic acids, etc. An interesting variation was used by Sorensen and co-worker's in a synthesis of FR182877,⁵⁶¹ in which Weinreb amide **598** was treated with LiCH₂P(O)(OMe)₂ (599) to give phosphonate ester 600. Weinreb amides have been seen to react with Grignard reagents (Sec. 8.4), and reduced to aldehydes (Sec. 4.6.C), and phosphonate anions give highly functionalized phosphonate esters. Such phosphonate esters can, of course, be used in subsequent olefination reactions (also see 584).



The use of phosphine oxide ylids and phosphonate ester carbanions just described is very similar to Corey's use of α -lithiophosphonic acid bis(amides) for olefination reactions. Corey showed

^{559.} Buss, A.D.; Warren, S. J. Chem. Soc. Chem. Commun. 1981, 100.

^{560. (}a) Earnshaw, C.; Wallis, C.J.; Warren S. J. Chem. Soc. Chem. Commun. 1977, 314; (b) Earnshaw, C.; Wallis, C.J.; Warren, S.T., J. Chem. Soc. Perkin Trans. 1 1979, 3099; (c) Davidson, A.H.; Warren, S. Ibid. 1976, 639.

^{561.} Vanderwal, C.D.; Vosburg, D.A.; Welle, S.; Sorensen, E.J. J. Am. Chem. Soc. 2003, 125, 5393.

that reaction of **601** with *n*-butyllithium gave the lithio derivative **602**.⁵⁶² Subsequent reaction with methyl 2,2-dimethylpropanoate (methyl pivaloate) gave the corresponding ketone, **603**. Reduction with LiAlH₄ and quenching with water led to isolation of alcohol **604**. Heating in refluxing benzene with silica gel, liberated the alkene **605** in 71% yield.⁵⁶⁰



Corey also showed that the stereochemistry of the alkene could be controlled. Reaction of **601** with butyllithium and then pivalaldehyde, for example, gave **606**. Thermal elimination gave a 3:1 (*Z*/*E*) mixture of **607** and **605** favoring **607**.⁵⁶³ By comparison, the triphenylphosphonium carbanion from 1-bromooctane reacted with pivalaldehyde to give a 98.5:1.5 mixture of **607/605**, which clearly favored the (*Z*)-isomer.⁵⁶³ Good yields of (*E*) or (*Z*) alkenes were obtained by oxidation of the alcohol intermediate derived from reaction with aldehydes or ketones, with manganese dioxide in chloroform. Sodium borohydride was used for reduction of this ketone, as shown above, allowing control the relative stereochemistry of the intermediate product.

$ \begin{array}{c} S \\ MeO - P \\ MeO \end{array} X \\ MeO \end{array} $	MeO - P - X MeO MeO
608	609

Corey and Kwiatkowski developed phosphonothioate derivative **608**⁵⁶⁴ and phosphonate derivative **609**, and showed the corresponding ylids gave good yields of alkene products upon reaction with aldehydes and ketones when X = Cl, C(=O) R, or Ar. When X = H or alkyl in **609** (the ylid is not stabilized),

formation of the lithio derivative was difficult and elimination to the alkene was also sluggish. The thio derivative (608), however, reacted with carbonyl derivatives and decomposed to alkene products at temperatures ranging from ambient to 65° C. An example is the reaction of 610 with *n*-butyllithium and then 1-bromobutane to give the alkylated product, 611. This result is unusual since Wittig-type reagents do not undergo alkylation reactions in good yield. Addition of more base to 611 gave a new ylid and condensation with benzophenone at 25° C, gave 612. Elimination to the alkene required higher temperatures (65° C) when the carbonyl component was a nonconjugated aldehyde or ketone.

^{562.} Corey, E.J.; Kwiatkowski, G.T. J. Am. Chem. Soc. 1966, 88, 5652.

^{563.} Corey, E.J.; Kwiatkowski, G.T. J. Am. Chem. Soc. 1966, 88, 5653.

^{564.} Corey, E.J.; Kwiatkowski, G.T. J. Am. Chem. Soc. 1966, 88, 5654.

$$\begin{array}{c} \begin{array}{c} S \\ MeO \\ / \\ MeO \\ 610 \end{array} \xrightarrow{H} MeO \\ 611 \end{array} \xrightarrow{H} MeO \\ \begin{array}{c} S \\ P \\ H \\ Ph \\ Ph \\ Ph \\ Ph \\ 612 \end{array} \xrightarrow{Ph \\ Ph \\ 612 \end{array} \xrightarrow{Ph \\ 612 \end{array} \xrightarrow{Ph \\ Ph \\ 612 \end{array} \xrightarrow{Ph \\ 612 \end{array}$$

The disconnection for the Wittig type reactions is



8.8.A.iv. Alkenylphosphonium Salts. Alkenylphosphonium salts are known, and they react with carbonyl compounds to form heterocyclic compounds. Phosphonium salt (613) was generated by reaction of 1-phenoxy-2-bromoethane with PPh₃, followed by heating.⁵⁶⁵ Phosphonium salt 614 was formed from the corresponding β -chloro- α , β -unsaturated ketone by reaction with PPh₃ and 613, followed by reaction with aqueous KBr.⁵⁶⁶ The most common use of these phosphonium salts is in a reaction with carbonyl

compounds that possess a nucleophilic atom at the β - or γ -position. Treatment of **615** with sodium hydride generated an alkoxide, and addition to **613** gave ylid **616** and intramolecular olefination reaction gave dihydrofuran derivative **617** in 50% yield.⁵⁶⁷ α -Thioketones react with vinyl phosphonium salts to give dihydrothiophenes. When 3-mercapto-1-phenyl-2-propanone reacted with Ph₃P=CMe₂, for example, the product was **618**.⁵⁶⁸ In a similar manner, pyrrole-2-carboxaldehyde (**619**) reacted with vinylphosphonium salts to give a 1,2*H*-pyrrolizine derivative (**620**).⁵⁶⁹



An interesting modification of this reaction generates a normal Wittig reagent by reaction of **613** with an organocuprate (sec. 8.7.A). Addition of dibutyl cuprate to **613** generated ylid **621**. Subsequent reaction with hexanal gave the expected alkene **622** as a 1:4 mixture of (Z/E) isomers.⁵⁷⁰

- 568. McIntosh, J.M.; Goodbrand, H.B. Tetrahedron Lett. 1973, 3157.
- 569. Schweizer, E.E.; Light, K.K. J. Am. Chem. Soc. 1964, 86, 2963.
- 570. Just, G.; O'Connor, B. Tetrahedron Lett. 1985, 26, 1799.

^{565.} Schweizer, E.E.; Bach, R.D. Org. Synth. 1968, 48, 129.

^{566.} Zbiral, E.; Rasberger, M. Hengstberger, H. Annalen 1965, 725, 22.

^{567. (}a) Schweizer, E.E.; Liehr, J.C. J. Org. Chem. 1968, 33, 583; (b) Schweizer, E.E.; Creasy, W.; Liehr, J.C.; Jenkins, M.E.; Dalrymple, D.L. Ibid. 1970, 35, 601; (c) Schweizer, E.E. J. Am. Chem. Soc. 1964, 86, 2744.

$$= \stackrel{\text{PPh}_{3}}{=} \text{Br} \xrightarrow{(n-C_{4}H_{9})_{2}CuLi}_{\text{THF, HMPA}} \xrightarrow{n-C_{4}H_{9}}_{\text{-}50^{\circ}C} \stackrel{\text{+}}{\xrightarrow{}} \text{PPh}_{3} \xrightarrow{(1. n-C_{5}H_{11}CHO)}_{2. \text{ aq NH}_{4}Cl} \xrightarrow{n-C_{4}H_{9}}_{622} \xrightarrow{n-C_{5}H_{11}}_{622}$$

8.8.B. Sulfur Ylids

8.8.B.i. Sulfonium and Sulfoxonium Ylids. Just as phosphines react with alkyl halides to give the corresponding phosphonium salt, sulfides (thioethers) react with alkyl halides to give the corresponding sulfonium salt.^{493,571} Ingold and Jessop reported sulfonium ylid **624** in 1930 (from the fluorene dimethylsulfonium salt 623), but this initially formed ylid rearranged to give 625⁵⁷² in a sulfur analog of the Sommelet-Hauser rearrangement⁵⁷³ (sec. 8.8.C.ii). It is now known that sulfur ylids are formed by reaction with a strong base⁵⁷⁴ (such as RO⁻/ROH, NaH/ DMSO, RLi, or LiNR₂ in THF or ether) with the appropriate sulfonium salt. The sulfonium salt is formed by reaction of a dialkyl sulfide or a diaryl sulfide (R₂S) with primary, allyl or benzyl halides⁵⁷⁵ The reaction of diphenyl sulfide and iodoethane gives sulfonium salt **626**.⁵⁷⁶ Subsequent reaction with *tert*-butyllithium generated the ylid (627), which contains the Ph_2S^+ moiety, a good leaving group for $S_N 2$ displacement by a nucleophile. The gegenion of the sulfonium salt is iodide, which can displace Ph₂S. In other words, the reaction that generates the sulfonium salt is reversible.⁵⁷⁷ The use of nonnucleophilic gegenions such as tetrafluoroborate or perchlorate is usually a necessity to minimize this side reaction. When highly electrophilic species such as silver salts are used, other complicating reactions are possible. Rearrangements can occur by reaction of $AgBF_4$ with the alkyl halide to form the secondary cation (sec. 12.2.B). The straight-chain sulfonium salt is usually the major product.⁵⁷⁸



- 571. Reference 492, pp 304-366.
- 572. (a) Ingold, C.K.; Jessop, J.A. J. Chem. Soc. 1930, 713; (b) Agami, C. Bull. Soc. Chim. Fr. 1965, 1021.
- 573. (a) Hilbert, G.E.; Pinck, L.A. J. Am. Chem. Soc. 1938, 60, 494; 1946, 68, 751; (b) Pine, S.H. Org. React. 1970, 18, 403.
- 574. Reference 493, pp 13-23, 29-33.
- 575. (a) Corey, E.J.; Chaykovsky, M. J. Am. Chem. Soc. 1965, 87, 1353; (b) Hatch, M.J. J. Org. Chem. 1969, 34, 2133; (c) LaRochelle, R.W.; Trost, B.M.; Kiepski, L. Ibid. 1971, 36, 1126; (d) Hauser, C.R.; Kantor, S.W.; Brasen, W.R. J. Am. Chem. Soc. 1953, 75, 2660; (e) Ratts, K.W.; Yao, A.N. J. Org. Chem. 1966, 31, 1185; (f) Speziale, A.J.; Tung, C.C.; Ratts, K.W.; Yao, A.N. J. Am. Chem. Soc. 1965, 87, 3460.
- 576. Corey, E.J.; Oppolzer, W. J. Am. Chem. Soc. 1964, 86, 1899.
- 577. (a) Ray, F.E.; Farmer, J. J. Org. Chem. 1943, 8, 391; (b) Ray, F.E.; Levine, I. Ibid. 1938, 2, 267.
- 578. (a) Trost, B.M.; Bogdanowicz, M.J. J. Am. Chem. Soc. 1973, 95, 5298; (b) Tang, C.S.F.; Rapoport, H. J. Org. Chem. 1973, 38, 2806.

$$\stackrel{\text{Ph}}{\stackrel{\text{S}}{\longrightarrow}} \xrightarrow{\text{Et} - I} \xrightarrow{\text{Ph}} \xrightarrow{\text{Ph}}_{\text{Ph}'} \xrightarrow{\text{t-BuLi or}} \xrightarrow{\text{Ph}}_{\text{LiNEt}_2, \text{THF}} \xrightarrow{\text{Ph}}_{\text{Ph}'} \xrightarrow{\text{e}}_{\text{627}}$$

Dimethyl sulfide is a useful precursor to sulfur ylids, reacting with iodomethane to give trimethylsulfonium iodide (628). When this salt was treated with *n*-butyllithium, deprotonation of the hydrogen on the α -carbon led to dimethylsulfonium methylid (629). Dimethyl sulfoxide also reacts with alkyl halides to give a sulfoxonium salt. When DMSO reacted with iodomethane, trimethylsulfoxonium iodide (630) was formed. As with the dimethyl sulfide derivative, treatment with a strong base such as *n*-butyllithium generated the corresponding ylid, dimethylsulfoxonium methylid (631).

$$\stackrel{\text{Me}}{\stackrel{\text{S}}{\longrightarrow}} \stackrel{\text{CH}_{3I}}{\stackrel{\text{Ne}}{\longrightarrow}} \stackrel{\text{Me}}{\stackrel{\text{S}}{\longrightarrow}} \stackrel{\text{I}}{\stackrel{\text{S}}{\longrightarrow}} \stackrel{\text{Me}}{\stackrel{\text{Ne}}{\longrightarrow}} \stackrel{\text{I}}{\stackrel{\text{S}}{\longrightarrow}} \stackrel{\text{Me}}{\stackrel{\text{S}}{\longrightarrow}} \stackrel{\text{I}}{\stackrel{\text{S}}{\longrightarrow}} \stackrel{\text{Me}}{\stackrel{\text{S}}{\longrightarrow}} \stackrel{\text{I}}{\stackrel{\text{S}}{\longrightarrow}} \stackrel{\text{Me}}{\stackrel{\text{S}}{\longrightarrow}} \stackrel{\text{I}}{\stackrel{\text{Me}}{\longrightarrow}} \stackrel{\text{I}}{\stackrel{\text{I}}{\stackrel{\text{Me}}{\longrightarrow}} \stackrel{\text{I}}{\stackrel{\text{Me}}{\longrightarrow}} \stackrel{\text{I}}{\stackrel{\text{I}}{\stackrel{\text{Me}}{\xrightarrow}} \stackrel{\text{I}}{\stackrel{\text{I}}{\stackrel{\text{I}}{\stackrel{\text{I}}} \stackrel{\text{I}}{\stackrel{\text{I}}} \stackrel{\text{I}}{\stackrel{\text{I}}} \stackrel{\text{I}}{\stackrel{\text{I}}} \stackrel{\text{I}}{\stackrel{\text{I}} \stackrel{\text{I}}{\stackrel{\text{I}}} \stackrel{\text{I}}{\stackrel{\text{I}} \stackrel{\text{I}}{\stackrel{\text{I}}} \stackrel{\text{I}}{\stackrel{\text{I}} \stackrel{\text{I}}{\stackrel{\text{I}} \stackrel{\text{I}} \stackrel{\text{I$$

When **629** reacts with carbonyl derivatives, it essentially behaves as a carbanion rather than an ylid. In a synthesis of aphidicolin by Toyota, Sasaki, and Ihara,⁵⁷⁹ the reaction of dimethylsulfonium methylid with ketone **632** gave the acyl addition product **633** as the initial product. Dimethyl sulfide (Me₂S) is a good leaving group, and the nearby alkoxide unit displaced Me₂S to give oxirane **634**, in 89% yield. Sulfur ylids normally react with aldehydes or ketones to generate an epoxide, and *not* an alkene.⁵⁸⁰ Dimethylsulfoxonium ylid **631** also reacts with carbonyl compounds to give an intermediate (**635**) that contains a leaving group, DMSO, and displacement by the adjacent alkoxide also gives an oxirane (**636**).⁵⁷⁵ An intermediate such as **633** or **635** was generated independently and shown to form an epoxide.⁵⁸¹



It is known that dimethylsulfonium methylid (629) adds irreversibly to ketones and aldehydes.

^{579.} Toyota, M.; Sasaki, M.; Ihara, M. Org. Lett. 2003, 5, 1193.

^{580.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 944-946.

^{581.} Johnson, C.R.; Schroeck, C.W.; Shanklin, J.R. J. Am. Chem. Soc. 1973, 95, 7424.

On the other hand, dimethylsulfoxonium methylid (**631**) adds reversibly. This difference is reflected in their reactivity with cyclic ketones such as 4-*tert*-butyl cyclohexanone (**637**). Dimethylsulfonium methylid (**629**) reacted with **637** to give the oxirane with an axial exocyclic C–C bond (**638**), which is less stable than the product with an axial C–O bond (**639**).⁵⁸² When **631** reacted with **637**,⁵⁸³ however, the oxirane with the more stable equatorial exocyclic C–C bond (**639**) was formed. This is attributed to the reversibility of the addition of **631** to the ketone leading to the more stable oxirane whereas **629** formed the intermediate salt irreversibly in what is essentially a kinetic process.



Another difference in the reactivity of these two ylids is reflected in their reactions with α , β -unsaturated ketones. The carboethoxy dimethylsulfonium methylid **640** reacted with cyclohexenone to give the usual alkoxy sulfonium salt **641**. Intramolecular displacement of dimethyl sulfide led to the expected oxirane (**642**), analogous to the formation of **634**. This product represents a generalized reaction, and dialkylsulfonium ylids react via 1,2-addition with displacement of the sulfide to give an allylic oxirane.⁵⁸¹ When carboethoxy dimethylsulfoxonium ylid **643** reacted with cyclohexenone, however, the 1,2-addition adduct was formed reversibly and 1,4-addition becomes competitive. The conjugate addition product **644** is an enolate anion (secs. 9.2, 9.3, 9.7) and intramolecular displacement of DMSO generated a cyclopropane ring, as in **645**.⁵⁸³ The latter reaction is more facile when the conjugate system becomes more



amenable to Michael addition. Acrylate **646**, for example, gave only a 9% yield of **647** after 1 h, whereas **648** gave a 91% yield of **649** under the same reaction conditions.⁵⁸⁴ The reaction is

^{582. (}a) Carlson, R.G.; Behn, N.S. J. Org. Chem. 1967, 32, 1363; (b) Johnson, C.R.; Katekar, R.A. J. Am. Chem. Soc. 1970, 92, 5753; (c) Johnson, C.R. Acc. Chem. Res. 1973, 6, 341.

^{583.} Reference 493, p 40.

^{584.} Landon, S.R.; Punja, N. J. Chem. Soc. C 1967, 2495.

synthetically useful despite the limitations, as shown by the conversion of R-(–)-carvone (650) to 651 in 96% yield as part of Brocksom and co-worker's synthesis of guaiane sesquiterpenes.⁵⁸⁵



Disconnections for reactions of these sulfur ylids are

$$\begin{array}{c|c} R^{1} & O \\ \searrow \\ R^{2} \end{array} R \end{array} \xrightarrow{O}_{R^{1}} R^{2} + R \xrightarrow{X} \qquad \begin{array}{c} R^{1} & O \\ R^{2} \end{array} \xrightarrow{R^{1}} R^{3} \end{array} \xrightarrow{O}_{R^{2}} R^{3} + R \xrightarrow{X} \end{array}$$

This methodology has been applied to a variety of synthetic applications.⁵⁸⁶ Epoxide **652** reacted with **629** to give the allylic alcohol **653**, in 77% yield, a step in Kadota and co-worker's synthesis of hemibrevetoxin B.⁵⁸⁷ Generating an oxirane in the presence of a nucleophile allows further reaction. Initial reaction of the ketone moiety of **654** with **631** gave the oxirane **655**. The nucleophilic nitrogen of imidazole opened the oxirane, however, to give **656**.⁵⁸⁸ The cyclopropanation reaction is also quite useful for derivatization of key compounds, as in the cyclopropanation of the *N*-methyluridine moiety in **657** with **631** generated the **658** in 80% yield (7:3 β/α).⁵⁸⁹



^{585.} de Faria, M.L.; de A. Magalhaes, R.; Silva, F.C.; de O. Matias, L.G.; Ceschi, M.A.; Brocksom, U.; Brocksom, T.J. *Tetrahedron: Asymmetry* **2000**, *11*, 4093.

- 587. Kadota, I.; Abe, T.; Ishitsuka, Y.; Touchy, A.S.; Nagata, R.; Yamamoto, Y. Tetrahedron Lett. 2007, 48, 219.
- 588. Chaykovsky, M.; Benjamin, L.; Fryer, R.I.; Meltesics, W. J. Org. Chem. 1970, 35, 1178.
- 589. Kunieda, T.; Witkop, B. J. Am. Chem. Soc. 1971, 93, 3478.

^{586.} Reference 493, pp 51-107.



8.8.B.ii. Diphenylcyclopropylsulfonium Derivatives. Trost and Bogdanowicz showed that diphenyl-cyclopropylsulfonium ylids such as **659** reacted with ketones and aldehydes in a manner similar to **629**. Attack at the carbonyl generated the expected intermediate **660**, and intramolecular displacement of diphenyl sulfide by alkoxide gave the oxirane **661**. This oxirane, however, is an oxaspiropentane derivative and is susceptible to several additional synthetic manipulations.^{590,593a} A useful transformation is the conversion of the oxaspiropentane moiety to cyclobutanone derivative (**662**) by treatment with Lewis acids such as HBF₄, LiClO₄, or Eu(fod)₃, where fod = tris(6,6,7,7,8,8,8)-heptafluoro-2,2-dimethyl-3,5-octanedionate.⁵⁹¹ Such products arise via a cationic rearrangement of an oxonium ion (sec. 12.2.B), formed by protonation of (or coordination to) the oxiranyl oxygen. Ring opening generated a cyclopropylcarbinyl cation, which rearranged to the oxo-stabilized cyclobutyl cation (sec. 12.2.B), and this gave the cyclobutanone product. When better coordinating Lewis acids are used [LiClO₄ or Eu(fod)₃], there is a chelation effect that further stabilizes the intermediate cation.



An alternative reaction pathway is available when a carbon adjacent to the oxiranyl moiety possesses a hydrogen. Reaction of **663** with lithium diisopropylamide (sec. 9.2.B) removed the hydrogen on the carbon α to the oxiranyl carbon and formed **664** via opening of the oxaspiro moiety. When this was done in the presence of chlorotrimethylsilane, the alkoxide was trapped as the trimethylsilyl ether **665** (sec. 7.3.A.i). Subsequent heating (flash vacuum pyrolysis at ~ 300-500°C) led to a rearrangement that generated **666**.⁵⁹² This so-called **vinyl cyclopropane rearrangement** is a signatropic rearrangement that will be discussed in sections 11.12.B and 13.9.C.iii. Silyl enol ether **666** is simply a protected enolate (secs. 9.2.B, 9.2.D) and aqueous hydrolysis liberated the unstable enol, **667** (sec. 7.3.A.i). Tautomerization favored the final product, ketone **668**.⁵⁹² Trost et al. applied this methodology to a synthesis of allamandin.⁵⁹³

592. Trost, B.M.; Bogdanowicz, M.J. J. Am. Chem. Soc. 1973, 95, 289.

^{590. (}a) Trost, B.M.; Bogdanowicz, M.J. J. Am. Chem. Soc. 1971, 93, 3773; (b) Trost, B.M.; LaRochelle, R.; Bogdanowicz, M.J. Tetrahedron Lett. 1970, 3449.

^{591.} Trost, B.M.; Keeley, D.; Bogdanowicz, M.J. J. Am. Chem. Soc. 1973, 95, 3068.

^{593. (}a) Trost, B.M.; Mao, M.K.-T.; Balkovec, J.M.; Buhlmayer, P. J. Am. Chem. Soc. 1986, 108, 4965; (b) Trost, B.M.; Balkovec, J.M.; Mao, M.K-T. Ibid. 1986, 108, 4974.



The disconnections for the cyclopropyl sulfide reactions are



8.8.C. Nitrogen Ylids^{494,594}

8.8.C.i. Formation of Nitrogen Ylids. The first report of a nitrogen ylid was probably by Krohnke in 1935, who prepared the resonance stabilized pyridinium ylid **669** by reaction of pyridinium salt **670** with potassium carbonate (K_2CO_3).⁵⁹⁵ Wittig and Wetterling⁵⁹⁶ found that phenyllithium reacted with tetramethylammonium bromide (**671**) to give the corresponding ylid (**672**). The ylid was shown to be the lithium bromide complex. Complexation with added or generated metal salts or other reagents is very important for the stability of nitrogen ylids. Ylid **672** decomposed to carbene (CH₂:) (see sec. 13.9) in solvents that strongly coordinate LiBr, and this carbene polymerized to polymethylene under the reaction conditions. In ether (ambient temperatures for 90 h), reaction of tetramethylammonium bromide (**671**) and phenyllithium gave 20% trimethylamine and 12% polymethylene. In dimethoxyethane (DME), **672** formed a strong complex with LiBr and polymethylene was formed in 74% yield. This result suggested that the free (uncomplexed) ylid was rather unstable.



Wittig showed that tetramethylammonium bromide (671) reacted with two equivalents of phenyllithium to form a species (672 and/or 673) that gave 18% of monosubstituted product (674) and 20% of the bis-adduct (675) on reaction with benzophenone followed by hydrolysis.⁵⁹⁷

^{594.} Reference 494, pp 251-283.

^{595.} Kröhnke, F. Berichte 1935, 68, 1177.

^{596.} Wittig, G.; Wetterling, M. Annalen 1947, 557, 193.

^{597. (}a) Wittig, G.; Rieber, M. Annalen 1949, 562, 177; (b) Wittig, G.; Polster, R. Ibid. 1956, 599, 1.



Although nitrogen ylids behave as carbanions, alkylation of 672 in THF is difficult because the carbanion is also basic and induces an elimination reaction with an alkyl halide (loss of trimethylamine). Reaction of 672 with bromocyclohexane, for example, gave a 92% yield

$$\begin{array}{c} Me \\ Me \\ Me \\ Me' \\ 672 \\ \hline \\ 2. \text{ HBr} \\ \hline \\ 1. \text{ PhCO}_2\text{Et, ether} \\ \hline \\ Me' \\ 676 \\ \hline \\ Me' \\ 676 \\ \hline \\ Me' \\ 676 \\ \hline \\ \end{array}$$

of cyclohexene.⁵⁹⁸ Ylid **672** does behave as a carbanion if the substrate does not possess a leaving group. Reaction with either benzonitrile or ethyl benzoate gave the ammonium ketone **676**.⁵⁹⁸ Similar reaction with benzoyl chloride

gave a mixture of the usual ketone product (676) and a secondary product resulting from O-alkylation of the enol form of the acid chloride. Nitrogen ylids behave as both a stronger base and a stronger carbanion than any of the phosphorus or sulfur ylids previously encountered.

Pyridinium ylids such as those discovered by Krohnke (see above) and simple *N*-alkyl derivatives generally undergo nucleophilic reactions as carbanions. Pyridinium ylids react with aldehydes in a Knoevenagel reaction (sec.



to give **678** after elimination of water from the initial alcohol product.^{596,597a,599} Pyridinium ylids⁶⁰⁰ undergo Michael addition on reaction with conjugated carbonyl systems. Another class of nitrogen ylids is azomethine ylids, which are useful synthetic intermediates and often formed by thermal ring opening of aziridine derivatives.⁶⁰¹ The main synthetic use of azomethine ylids is in [3+2]-cycloadditions and this will be discussed in Section 11.11.F.⁶⁰²

^{598. (}a) Weygand, F.; Daniel, H.; Schroll, A. *Berichte* **1964**, *97*, 1217; (b) Weygand, F.; Daniel, H. *Ibid.* **1961**, *94*, 3147.

^{599.} Also see (a) Kröhnke, F. Chem. Ber. 1951, 84, 388; (b) Idem, Ibid. 1950, 83, 253.

 ^{600. (}a) Zecher, W.; Kröhnke, F. *Berichte* 1961, 94, 690; (b) Kröhnke, F.; Zecher, W.; Curtze, J.; Drechsler, D.; Pfleghar, K.; Schnalke, K.E.; Weis, W. *Angew. Chem.* 1962, 74, 811.

^{601.} Huisgen, R.; Scheer, W.; Mäder, H.; Brunn, E. Angew. Chem. Int. Ed. 1969, 8, 604.

^{602. (}a) Lown, J.W. Recent Chem. Progr. 1971, 32, 51 [Chem. Abstr. 76:3599g 1972]; (b) Kellogg, R.M.; Tetrahedron 1976, 32, 2165; (c) Huisgen, R. J. Org. Chem. 1976, 41, 403; (d) Hermann, H.; Huisgen, R.; Mäder, H. J. Am. Chem. Soc. 1971, 93, 1779; (e) Fleming, I. Frontier Orbitals and Organic Chemical Reactions, Wiley-Interscience, London, 1976, pp 109-110, 148-160.

8.8.C.ii. The Stevens' Rearrangement and the Sommelet Rearrangement. The intermediacy of nitrogen ylids has been suggested for two classical reactions, the **Stevens' rearrangement**^{603,573c} and the **Sommelet-Hauser rearrangement** (sometimes called the **Sommelet rearrangement**).⁶⁰⁴ Stevens found that treatment of phenacylbenzyldimethylammonium bromide (**679**) with aqueous hydroxide gave amino ketone **682** The reaction probably proceeds via hydrogen abstraction from the ammonium salt (**679**) to give the ylid **680**. A N \rightarrow C 1,2-benzyl shift occurs via a carbanionic intermediate **681** to give amine **682**.^{603e} The mechanism⁶⁰⁵ involves a [2,3]-sigmatropic rearrangement of the ylid, followed by proton migration to restore aromaticity. The preparation of complex alkaloids is a common synthetic application of the Stevens' rearrangement. The reaction of bis(α, α -o-xylylene) ammonium bromide (**683**) with phenyllithium led to the α -lithio compound **684**. This nitrogen ylid was unstable and rearranged with loss of LiBr, to **685**.⁶⁰⁶



Formation of *o*-benzylbenzyldimethylamine (**689**) from benzhydryltrimethylammonium bromide (**686**),⁶⁰⁴ on heating to 180°C with concentrated hydroxide, illustrates the Sommelet rearrangement. Initial deprotonation probably occurred at the benzylic site, but equilibrium conditions generated ylid **687**. Nucleophilic attack at the proximal benzene ring gave **688** via cleavage of the C–N bond, and subsequent aromatization gave the final product **689**. Evidence suggests the mechanism is a [1,2]-shift of the ylid via a caged radical pair intermediate.⁶⁰⁵

^{603. (}a) Stevens, T.S.; Creighton, E.M.; Gordon, A.B.; MacNicol, M. J. Chem. Soc. 1928, 3193; (b) Stevens, T.S. *Ibid.* 1930, 2107; (c) Thomson, T.; Stevens, T.S. J. Chem. Soc. 1932, 55; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-89; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 618-619.

^{604. (}a) Sommelet, M. Compt. Rend. 1937, 205, 56; (b) Hauser, C.R.; van Eenam, D.N. J. Am. Chem. Soc. 1956, 78, 5698; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-88; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 608-609.

^{605. (}a) Tanaka, T.; Shirai, N.; Sugimori, J.; Sato, Y. J. Org. Chem. 1992, 57, 5034; (b) Lepley, A.R.; Giumanini, A.G. in Mechanism of Molecular Migrations, Vol. 3; Thyagarajan, B.S. (Ed.), Wiley-Interscience, New York, 1971, p 297.

^{606.} Wittig, G.; Tenhaeff, H.; Schoch, W.; Koenig, G. Annalen 1951, 572, 1.

Steric effects appear to be less significant than electronic effects for ylid stability.⁶⁰⁷ The **ortho substitution rearrangement**⁶⁰⁸ involves reaction of benzyltrimethylammonium salt **690** with NaNH₂ to give 2-(dimethylaminomethyl)toluene (**691**). This rearrangement is either the same reaction as the Sommelet rearrangement, or closely related.⁶⁰⁸ Hauser and Jones showed that this rearrangement could be used for a ring expansion,⁶⁰⁹ where reaction of dimethylammonium salt **692** with sodium amide gave an 83% yield of **693**.



The Sommelet and Stevens rearrangements compete with each other in some cases, as shown in Table 8.21.⁶¹⁰ The major products from reaction of **694** with base are the Stevens products **696** and **697**, and the Sommelet-Hauser product **698**. Small amounts of the para rearrangement product (**699**) and the direct displacement product (**700**) are also present. The ammonium salt precursor to the ylid (**694**) can generate either ylid (**695** or **701**), but formation of **701** is sterically inhibited relative to **695**. The Stevens product of **701** (amine **702**) is more sterically crowded than **696** or **697**. In polar aprotic solvents the major product is the Sommelet-Hauser product **698**, but in nonpolar solvents (hexane) the Stevens product **696** predominates. In DMSO, the base is more nucleophilic. leading to the displacement product **700** in high yield. Alkoxide bases are not strong enough to generate the ylid from **694**, and the displacement reaction (to give **700**) dominates in those cases.

^{607.} Heard, G.L.; Yates, B.F. Aust. J. Chem. 1994, 47, 1685.

 ^{608. (}a) Kantor, S.W.; Hauser, C.R. J. Am. Chem. Soc. 1951, 73, 4122; (b) Puterbaugh, W.H.; Hauser, C.R. Ibid. 1964, 86, 1105.

^{609.} Jones, G.C.; Hauser, C.R. J. Org. Chem. 1962, 27, 3572.

^{610.} Pine, S.H.; Munemo, E.M.; Phillips, T.R.; Bartolini, G.; Cotton, W.D.; Andrews, G.C. J. Org. Chem. 1971, 36, 984.



 Table 8.21. Competition Between the Sommelet and Stevens Rearrangements

Note that a nitrogen ylid has been invoked in the **Hofmann elimination reaction** (sec. 2.9.C.i).⁶¹¹ This ylid mechanism is highly questionable for many substrates⁶¹² that proceed via β -elimination with a coordinated hydroxide. In those cases, removal of the hydrogen directly by hydroxide appears more likely. The ylid mechanism probably operates when PhLi is used as a base⁶¹³ and there is steric inhibition of the usual β -elimination process.⁶¹⁴

The useful disconnections of nitrogen ylids are



8.8.D. Transition Metal Olefination Reagents

Other organometallic derivatives give Wittig-type olefination reactions, and titanium derivatives

614. Cope, A.C.; Mehta, A.S. J. Am. Chem. Soc. 1963, 85, 1949.

^{611.} Cope, A.C.; Ciganek, E.; LeBel, N.A. J. Am. Chem. Soc. 1959, 81, 2799.

^{612.} Reference 494, p 277-281.

^{613.} Wittig, G.; Polster, R. Annalen 1956, 599, 13.

are the most commonly used.⁶¹⁵ The initial addition reaction to the carbonyl gives a transient metalated alcohol that leads to an alkene. An example is the **Tebbe reagent**, which exists as a



bridged methylene species (see **703**) where Cp is cyclopentadienyl,⁶¹⁶ and the reaction with carbonyl compounds that leads to alkene derivatives is called **Tebbe olefination** The aluminum species can be varied

to include chloride (AlCl₃), triperdeuteromethyl aluminum $[Al(CD_3)_3]$ or trimethylsilyl $[AlCl(CH_2SiMe_3)_2]$. The most common reagent is the aluminum dimethylaluminum chloride compound shown. The Tebbe reagent reacts with ketones or aldehydes to give an alkene, analogous to the Wittig reagent. In a synthesis of (+)-hygrine, Jew, Park and co-worker's converted aldehyde **704** to alkene **705** in 82% yield using the Tebbe reagent in THF.⁶¹⁷



The Tebbe reagent is quite useful in that it reacts with the carbonyl of esters or lactones to give vinyl ethers, in contrast to common Wittig reagents. For example, in a synthesis of the C17-C28 fragment of spongistatin 1, Roush and Holson converted ester **706** to vinyl ether **707** in 74% yield.⁶¹⁸ The Tebbe reagent also reacts with conjugated esters via 1,2-addition to give the vinyl ether.^{616a}



Other titanium-based olefination reagents have been developed. Eisch used a zinc analog of the Tebbe reagent (**708**) in a reaction with benzophenone to give 1,1-diphenylethene in 78% yield.⁶¹⁹ Similarly, Clawson, Buchwald and Grubbs used **709**



^{615.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd Ed. Wiley-VCH, New York, 1999, pp 341-350.

^{616. (}a) Tebbe, F.N.; Parshall, G.W.; Reddy, G.S. J. Am. Chem. Soc. 1978, 100, 3611; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-93; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, p. 856.

^{617.} Lee, J.-H.; Jeong, B.S.; Ku, J.-M.; Jew, S.-s.; Park, H-g. J. Org. Chem. 2006, 71, 6690.

^{618.} Holson, E.B.; Roush, W.R. Org. Lett. 2002, 4, 3719.

^{619.} Eisch, J.J.; Piotrowski, A. Tetrahedron Lett. 1983, 24, 2043.

in olefination reactions with ketones and aldehydes.⁶²⁰ Alkoxy-titanium reagents such as **710** have been employed, as in the conversion of cyclohexane carboxaldehyde to 1-cyclohexyl-1,3-butadiene (**711**) in 86% yield (96:4 Z/E).⁶²¹

$$\bigcirc \text{CHO} + \bigcirc \overset{\text{Oi-Pr}}{=} \overset{\text{I.}-78 \to 0^{\circ}\text{C}}{\overset{\text{Oi-Pr}}{\text{710}}} \xrightarrow{\text{I.}-78 \to 0^{\circ}\text{C}} \overbrace{\text{2. Mel, 0^{\circ}\text{C}}}^{\text{Oi-Pr}} \xrightarrow{\text{711}}$$

Other titanium reagents have been used for olefination reactions. Petasis developed Cp₂TiMe₂ (713), now called the **Petasis reagent**.⁶²² The Petasis reagent is prepared by reaction of methyllithium with titanocene dichloride (Cp₂TiCl₂)], which avoids some of the difficulties of 703 (high cost, long preparation times, short shelf-lives, extreme sensitivity to air and water, residual aluminum reagents). Aldehydes and ketones react with the Petasis reagent to give an alkene, illustrated by the conversion of 712 to 714 in 76% yield, taken from Smith and coworker's synthesis of (+)-phorboxazole A.⁶²³ Note that the ketone moiety reacted in preference ot the carbony of the thioester. Petasis proposed that olefination proceeds via methyl transfer from an intermediate such as 715.⁶²⁴



Hughes proposed that olefination of esters proceeds via a titanium carbene such as **716**, and an oxatitanacycle **717**.⁶²⁵ This latter proposal has independent support, based on mass spectrometry evidence provided by Pilli, Eberlin and co-workers.⁶²⁶ In the absence of an aldehyde or ketone moiety, an ester moiety can react. An example is the conversion of the lactone unit in **718** to the vinyl ether in **719** (85% yield) in a synthesis of (–)-kendomycin by Smith and co-workers.⁶²⁷



- 620. Clawson, L.; Buchwald, S.L.; Grubbs, R.H. Tetrahedron Lett. 1984, 25, 5733.
- 621. Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, V. Tetrahedron Lett. 1983, 24, 4029.
- 622. Petasis N.A.; Bzowej, E.I. J. Am. Chem. Soc. 1990, 112, 6392.
- 623. Smith III, A.B.; Razler, T.M.; Ciavarri, J.P.; Hirose, T.; Ishikawa, T. Org. Lett. 2005, 7, 4399.
- 624. Petasis N.A.; Bzowej, E.J. J. Org. Chem. 1992, 57, 1327.
- 625. Hughes, D.L.; Payack, J.F.; Cai, D.; Verhoeven, T.R.; Reider, P.J. Organometallics, 1996, 15, 663.
- 626. Meurer, E.C.; Santos, L.S.; Pilli, R.A.; Eberlin, M.N. Org. Lett. 2003, 5, 1391.
- 627. Smith III, A.B.; Mesaros, E.F.; Meyer, E.A. J. Am. Chem. Soc. 2006, 128, 5292.



A Petasis-like reagent has also been reported that gives the same reaction: $CH_2(ZnI)_2$, $TiCl_2$, and TMEDA in THF.⁶²⁸ Oshima and co-workers developed a TiCl₄ reagent (Zn-CH₂Br₂-TiCl₄)⁶²⁹ that gave olefination. It was electrophilic and generally suppressed the tendency of a ketone substrate to enolize. Lombardo developed a more active form of this reagent by dropwise addition of TiCl₄ to a stirred suspension of zinc dust in CH₂Br₂ and THF at -40°C, followed by warming the mixture to 5°C and *stirring for 3 days*.⁶³⁰ Lombardo used this reagent in synthetic studies of C₂₀ gibberellins (GA₃₈).⁶³⁰

Mehta and Islam used Lombardo's reagent to convert **720** to **721**, in 71% yield, in a synthesis of ottelione.⁶³¹ Lombardo's modified reagent is particularly important when the ketone or

$$\begin{array}{c} H \\ \hline H \\ \hline$$

aldehyde to be used in the olefination reaction is sensitive to basic reagents. Another variation of this reagent uses CH_2Br_2 , Zn, Ti Cl_4 and a catalytic amount of $PbCl_2$.⁶³²

The **Nysted reagent** (722)⁶³³ is commercially available, and it reacts with aldehydes or ketones in the presence of BF₃•etherate to give an alkene. Reaction with 2-phenylpropanal, for example, gave an 82% yield of 723.⁶³⁴ The **Takai reaction**⁶³⁵ uses an alkyl di-or triiodide in the presence of CrCl₂ to generate the alkene. An example is taken from Huang and co-worker's synthesis of psymberin, in which aldehyde 724 was converted to the vinyl iodide 725 in 90% yield as a 5:1 E/Z mixlure.⁶³⁶

^{628.} Matsubara, S.; Ukai, K.; Mizuno, T.; Utimoto, K. Chem. Lett. 1999, 825.

^{629.} Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. Tetrahedron Lett. 1978, 2417.

^{630. (}a) Lombardo, L. Tetrahedron Lett. 1982, 23, 4293; (b) Lombardo, L. Org. Synth. Coll. Vol. 8 1993, 386.

^{631.} Mehta, G.; Islam, K. Angew. Chem. Int. Ed. 2002, 41, 2396.

⁽a) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. J. Org. Chem. 1994, 59, 2668; (b) Takai, K.; Kataoka, Y.; Miyai, J.; Okazoe, T.; Oshima, K.; Utimoto, K. Org. Synth., 1995, 73, 73. For a synthetic example taken from a synthesis of (-)-periplanone B, see Hodgson, D.M.; Foley, A.M.; Boulton, L.T.; Lovell, P.J.; Maw, G.N. J. Chem. Soc. Perkin Trans. 1 1999, 2911.

^{633. (}a) Nysted, L.N. US Patent 3 865 848, 1975 [Chem. Abstr. 1975, 83:10406q]; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, p. 826.

^{634.} Matsubara, S.; Sugihara, M.; Utimoto, K. Synlett 1998, 313.

^{635. (}a) Takai, K.; Nitta, K.; Utimoto, K. J. Am. Chem. Soc. 1986, 108, 7408; (b) Okazoe, T.; Takai, K.; Utimoto, K. J. Am. Chem. Soc. 1987, 109, 951; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 640-641.

^{636.} Huang, X.; Shao, N.; Palani, A.; Aslanian, R.; Buevich, A. Org. Lett. 2007, 9, 2597.



Other organometallic reagents have been reported to give Wittig-type olefination reactions with ketones and aldehydes. Typical examples are **726**,⁶³⁷ **727**,⁶³⁸ **728**,⁶³⁹ **729**,⁶⁴⁰ and **730**.⁶⁴¹ This list is certainly not exhaustive, and is probably not completely representative. It does, however, illustrate some of the reagent types that have appeared, and continue to appear.

$$(MeS)_{2}B=CH_{2} Cl_{3}Mo=CH_{2} Cp \xrightarrow{PPh_{3}} I O-t-Bu Me_{2}Te-CHCO_{2}Et$$

$$726 727 Cp \xrightarrow{I} 728 729 I t-Bu 730$$

The disconnections for these reagents are identical to those in sec. 8.8.A for the Wittig reagents.

8.9. OTHER ORGANOMETALLIC CARBANIONIC COMPOUNDS

8.9.A. Organoiron Compounds

8.9.A.i. Formation and Stability. A few organoiron compounds have found their way into organic synthesis.⁶⁴² In general, Fe–C bonds are sensitive to homolytic cleavage, producing organic radicals and the metal in a lower oxidation state. This instability is due to small energy differences between the filled *d* orbitals, and the valence *s* and *p* anti-bonding orbitals of the Fe–C bond. This bond can be stabilized in at least two ways. The first involves addition of a ligand possessing acceptor properties (CO, cyclopentadienyl, phosphines, amines, etc.). The second involves alteration of the effective electronegativity of the carbon (induce a different hybridization state), or attachment of strongly electronegative groups such as fluorine to the carbon.

^{637.} Pelter, A.; Singaram, B.; Wilson, J.W. Tetrahedron Lett. 1983, 24, 635.

^{638.} Kauffmann, T.; Ennen, B.; Sander, J.; Wieschollek, R. Angew. Chem. Int. Ed. 1983, 22, 244.

^{639.} Clift, S.M.; Schwartz, J. J. Am. Chem. Soc. 1984, 106, 8300.

^{640. (}a) Aguero, A.; Kress, J.; Osborn, J.A. J. Chem. Soc. Chem. Commun. 1986, 531; (b) Freudenberger, J.H.; Shrock, R.R. Organometallics 1986, 5, 398.

^{641.} Osuka, A.; Mori, Y.; Shimizu, H.; Suzuki, H. Tetrahedron Lett. 1983, 24, 2599.

^{642.} Davies, S.G. Organotransition Metal Derivatives: Applications to Organic Synthesis, Pergamon Press, Oxford, 1982.

The iron must eventually be removed from the molecule to be useful in organic synthesis. Cleavage⁶⁴³ by a proton source is one way to break the Fe–C bond. Reaction with either water or an alcohol is usually sufficient, although a catalytic amount of acid is sometimes required.⁶⁴³ This process simply protonates the alkyl fragment in an organoiron compound such as **731** to give methane and **732**.⁶⁴³ Some organoiron complexes are thermally labile, generating an alkene via β -elimination.⁶⁴⁴ Thermal disproportionation is also observed and the thermal stability of simple alkyl groups in RFe(CO)₂Cp was reported to be R = Me \approx Ph >> Et > *i*-Pr. An example of the disproportionation reaction is the fragmentation of **733** to the alkene. Reaction of the organoiron complex with an halogen⁶⁴³ also cleaves the C–Fe bond. When **735** was treated with iodine, an alkyl halide (R–I) and the iron iodide (**735**) were formed. The two most common methods for converting an organoiron to the alkyl fragment are protonolysis and halogenation. Both of these techniques will be used in the following sections.

8.9.A.ii. Cyclopentadienylirondicarbonyl (Fp) Compounds. Cyclopentadienylbis(carbo nyliron) (Fp, 737)A is a common organoiron reagent.⁶⁴⁵ This derivative can be converted to an alkyl derivative (739, where R = alkyl) by reaction with an alkyl halide, or to the protio derivative (739, R = H) by reaction with an acid.⁶⁴⁶ The anionic reagent 738 is prepared by reaction of iron pentacarbonyl with the dimer of cyclopentadiene (736, sec. 115.B) at 200°C to give the dimeric species 737. Treatment of 737 with base leads to loss of cyclopentadiene and formation of 738. A byproduct of this process is ferrocene (740) formed by extrusion of carbon monoxide from 737.⁶⁴⁶

$$Fe(CO)_{5} + \left[\begin{array}{c} \hline \\ Fe(CO)_{2} \end{array} \right]_{2} \xrightarrow{Fe(CO)_{2}} \begin{bmatrix} Fe(CO)_{2} & Na \\ \hline \\ 738 & 739 \\ \hline \\ 739 & 739 \\ \hline \\ 740 & 740 \\ \hline \\ 740 & 740$$

The protonated form of Fp can add to conjugated carbonyl derivatives such as acrylonitrile⁶⁴⁷ and also with conjugated dienes.⁶⁴⁸ Both SO₃⁶⁴⁹ and carbon monoxide can be inserted into the Fe-C bond of FpR.⁵⁹⁸ Protonolysis provides a synthetic route to substituted nitriles or alkenes.

- 644. Braterman, P.S.; Cross, R.J. J. Chem. Soc. Dalton Trans. 1972, 657.
- 645. Eisch, J.J.; King, R.B. Organomet. Synth. 1965, 1, 114, 152.
- 646. Cotton, F.A.; Wilkinson, G.; Murillo, C.A.; Bochmann, M. *Advanced Inorganic Chemistry, 6th. Ed.*, Wiley, New York, *1999*. pp.808-812.
- 647. Green, M.L.H.; Nagy, P.L.I. J. Chem. Soc. 1963, 189
- 648. Ariyaratne, J.K.P.; Green, M.L.H. J. Chem. Soc. 1963, 2976
- 649. Bibler, J.P.; Wojcicki, A. J. Am. Chem. Soc. 1964, 86, 5051

^{643.} Piper, T.S.; Wilkinson, G. J. Inorg. Nucl. Chem. 1956, 3, 104.

In each case the Fp unit can also be removed photochemically, thermally, or by treatment with triphenylphosphine. Hydride extraction to give an alkene or a diene is also known.⁶⁵⁰

8.9.A.iii. Sodium Tetracarbonyl Ferrate. An extremely useful organoiron reagent is sodium tetracarbonyl ferrate $[Na_2Fe(CO)_4]$,⁶⁵¹ usually prepared by reduction of iron pentacarbonyl. The synthetic utility of this reagent lies in its ability to react with alkyl halides in a stepwise manner, including the reaction with two different alkyl halides as reported independently by Cooke and by Collman and co-workers.^{651,652} When sodium tetracarbonyl ferrate reacted with 1-bromooctane, a trigonal bipyramidal complex (741) was formed by insertion of the alkyl fragment.

$$Fe(CO)_5 \xrightarrow{1\% Na(Hg)} Na_2Fe(CO)_4$$

Subsequent treatment with iodoethane led to a second insertion and expansion of the coordination shell to an octahedral species (742). When the reaction was pressurized with carbon monoxide, CO was inserted in the C–Fe bond to give an acyl derivative 743. Protonolysis with acetic acid cleaved the Fe–C bond, and concomitant migration led to coupling of the alkyl and acyl fragments to produce 3-undecanone, along with iron tricarbonyl [Fe(CO)₃]. When 741 was treated with triphenylphosphine, CO insertion occurred via an intramolecular migration and protonolysis led to 3-undecanone.

The sequence shown above generates an unsymmetrical ketone. A modification of this reaction involves addition of only one alkyl halide to sodium tetracarbonyl ferrate, followed by pressurization with carbon monoxide.

Reaction with 1-bromohexane gave the expected complex, **744**. When treated with carbon monoxide, carbonyl insertion gave **745** and subsequent oxidation with oxygen in the presence of a base led to heptanoic acid.⁶⁵³ Iodination in the presence of water also gave the acid but when the reaction was done in ethanol, ethyl heptanoate was formed. Similarly, *N*,*N*-diethylheptanamide was generated by reaction with iodine and diethylamine.⁶⁵³ In general, the

^{650.} Green, M.L.H.; Smith, M.J. J. Chem. Soc. A, 1971, 3220

^{651.} Cooke, Jr., M.P. J. Am. Chem. Soc. 1970, 92, 6080

^{652. (}a) Collman, J.P.; Winter, S.R.; Clark, D.R. J. Am. Chem. Soc. 1972, 94, 1788; (b) Johnson, B.F.G.; Lewis, J.; Thompson, D.J. Tetrahedron Lett. 1974, 3789; (c) Cooke, Jr., M.P.; Parlman, R.M. J. Am. Chem. Soc. 1975, 97, 6863

⁽a) Collman, J.P.; Winter, S.R.; Komoto, R.G. J. Am. Chem. Soc. 1973, 95, 249; (b) Watanabe, Y.; Yamashita, M.; Mitsudo, T.; Tanaka, M.; Yakegami, Y. Tetrahedron Lett. 1973, 3535; (c) Yamashita, M.; Watanabe, Y.; Mitsudo, T.; Takegami, Y. Ibid. 1976, 1585

yields of ketone were higher with primary aliphatic halides and tosylates. Secondary substrates gave significant amounts of elimination, although this could be minimized if THF was used as a solvent.

$$\operatorname{Na_2Fe}(\operatorname{CO})_4 \xrightarrow{n-C_6H_{13}\operatorname{Br}} \left[\begin{array}{c} n-C_6H_{13} \\ 0 \\ -Fe \\ CO \\ 0 \\ -Fe \\ -CO \\ -FE \\ -C$$

The disconnection for this process is

$$\underset{R}{\overset{O}{\longrightarrow}} \underset{R^1}{\overset{R^1}{\longrightarrow}} \underset{R}{\overset{R-X}{\longrightarrow}} + \underset{R^1-X}{\overset{R^1-X}{\longrightarrow}} + \underset{CO}{\overset{CO}{\longrightarrow}}$$

8.9.A.iv. Chiral Organoiron Species. In work reported independently by Davies and by Liebeskind, iron reagents such as 746 were prepared, shown to be chiral and resolved into the (*R*) and (*S*) antipodes. One of the phenyl groups in 746 effectively blocks one face of the carbonyl moiety, inducing high diastereoface selection in reactions at that carbonyl or at the adjacent carbon. The carbonyl partner of the iron species can undergo enolate reactions similar to those of an acid derivative (secs. 9.2, 9.3). Oxidation with iodine or bromine, as shown above,⁶⁵³ cleaves the C–Fe bond and generates the acid derivative. Davies et al.⁶⁵⁴ showed that the asymmetric acetyl derivative 746 can be deprotonated to form an enolate and condensed with an aldehyde (such as propanal) or alkylated (as with iodomethane). Reaction of 746 with butyllithium and then propanal led to a second reaction with excess butyllithium, followed by alkylation with iodomethane and oxidation of the C–Fe bond with bromine gave 747 with high



asymmetric induction.^{654,655} Liebeskind and Welker reacted **746** with lithium diisopropylamide (sec. 9.2.A) and propanal, and showed that the enantioselectivity in the final β -hydroxy acids (**748**)

⁽a) Davies, S.G.; Dordor-Hedgecock, I.M.; Warner, P.; *Tetrahedron Lett.* 1985, 26, 2125; (b) Ambler, P.W.; Davies, S.G. *Ibid.* 1985, 26, 2129; (c) Davies, S.G.; Dordor, I.M.; Walker, J.C.; Warner, P. *Ibid.* 1984, 25, 2709; (d) Davies, S.G.; Dordor, I.M.; Warner, P. J. Chem. Soc. Chem. Commun. 1984, 956.

^{655.} Davies, S.G.; Walker, J.C. J. Chem. Soc. Chem. Commun. 1985, 209.

and **749**) was dependent on the conditions used to form the enolate.⁶⁵⁶ If diisobutylaluminum chloride (*i*-Bu₂AlCl) was used, a 5.2:1 mixture of **748** and **749** was reversed (to 1:11.6), in 66% yield. The iron group is a chiral auxiliary,⁶⁵⁷ where the acyl iron derivative behaves essentially as a protected acid. The chiral iron moieties are useful variation of enolate condensation chemistry (sec. 9.4.B). In addition to the formation of the condensation product, the high asymmetric induction will prove valuable.

The disconnections possible with these organoiron compounds are

$$\xrightarrow{HO_2C} \stackrel{R}{\underset{R^1}{\longrightarrow}} \stackrel{R}{\underset{HO_2C}{\longrightarrow}} \stackrel{R}{\underset{R^1}{\longrightarrow}} \stackrel{R^1}{\underset{R^2}{\longrightarrow}} \stackrel{R^2}{\underset{R^1}{\longrightarrow}} \stackrel{HO_2C}{\underset{R^2}{\longrightarrow}} \stackrel{R}{\underset{R^2}{\longrightarrow}} \stackrel{R}{\underset{R^$$

8.9.B. Organoaluminum Compounds

The chemistry of organoaluminum compounds is electrophilic in nature. Zweifel and Whitney, however, showed that conversion of an organoaluminum to its *ate* complex⁶⁵⁸ changed it into a nucleophilic species. Examples of this reaction have been largely confined to the vinyl alanates, which react with electrophiles to give the (*E*) or the (*Z*) isomer, depending on the reaction conditions. Treatment of an alkyne such as 3-hexyne with diisobutylaluminum hydride (DIBAL–H) gave vinyl alanate **750**. When **750** reacted with methyllithium, aluminate **751** formed in 73% yield. Subsequent reaction with an electrophile such as carbon dioxide led to a transfer of the vinyl group to the carbonyl, forming the (*E*)-acrylic acid derivative **752**.



The geometry of the intermediate alanate, and the final product was changed by first reacting methyllithium with Dibal to give the aluminate **753**. When this *ate* complex reacted with the alkyne (3-hexyne), a new *ate* complex (**754**) was formed. Subsequent reaction with carbon dioxide gave (Z)-acrylate **755**. The aluminum *ate* complex also reacted with alkynes, and

^{656.} Liebeskind, L.S.; Welker, M.E. Tetrahedron Lett. 1984, 25, 4341.

^{657. (}a) Liebeskind, L.S.; Welker, M.E. *Tetrahedron Lett.* **1985**, *26*, 3079; (b) Davies, S.G.; Easton, R.J.C.; Gonzalez, A.; Preston, S.C.; Sutton K.H.; Walker, J.C. *Tetrahedron* **1986**, *42*, 3987.

^{658. (}a) Zweifel, G.; Whitney, C.C. J. Am. Chem. Soc. 1967, 89, 2753; (b) Zweifel, G.; Steele, R.R. Ibid. 1967, 89, 2754, 5085.

hydrolysis converted the intermediate into substituted 1,3-butadienes.⁶⁵⁹ Reaction of the *ate* complex with halogens gave the corresponding vinyl halide, with retention of the geometry observed in the complex.⁶⁵⁸ Similar reaction with alkyl halides gave the substitution product.⁶⁶⁰ Vinyl alanates generated in this way can be quenched with other electrophiles. In a synthesis of (+)-testudinariol A, Amarasinghe and Montgomery converted a silyl-alkyne to a vinyl bromide by reacting the alkyne unit with Dibal (sec. 4.6.C) followed by bromination with Br₂.⁶⁶¹



Vinyl alanes are also generated by the transition metal catalyzed addition of trialkylaluminum reagents to alkynes. In Hoye and co-worker's synthesis of elenic acid,⁶⁶² 1-dodecyne reacted with Me₃Al and Cp₂ZrCl₂ and then MeLi. The resulting *ate* complex **756** then reacted with triflate **757** to give a 96% yield of the alkene, **758**.

$$C_{10}H_{21} \longrightarrow \underbrace{\begin{array}{c}1. Me_{3}Al}{Cp_{2}ZrCl_{2}} \\ 2. MeLi \end{array} \left[\begin{array}{c}Me \\ C_{10}H_{21} \\ 1. TfO \\ C_{10}H_{21} \\ 1. TfO \\ 2. aq NaHCO_{3} \end{array} \right]^{-1} Li^{+} \underbrace{\begin{array}{c}Me \\ 1. TfO \\ 2. aq NaHCO_{3} \\ C_{10}H_{21} \\ 1. TfO \\ 1. TfO \\ C_{10}H_{21} \\ 1. TfO \\ 0. TfO$$

The disconnection for the alkyne-alanate reaction is

$$X \xrightarrow{R} R \xrightarrow{R} R + X$$

8.9.C. Organochromium Reagents

Benzene and its derivatives react with chromium hexacarbonyl $[Cr(CO)_6]^{663}$ to give an arylchromium complex, **759**. Chromium resides in a position perpendicular to the plane of the ring, as shown. Semmelhack and co-workers found that the chromium activated the benzene ring to metal-hydrogen exchange with organolithium reagents (sec. 8.5.G), and these new lithium reagents reacted with alkyl halides to give the alkyl substitution product. As shown in Table 8.22,⁶⁶⁴ reaction of **759** with butyllithium generated **760** via lithium-hydrogen exchange. Subsequent reaction with an electrophile gave **761** in good yield.

^{659. (}a) Zweifel, G.; Polston, N.L.; Whitney, C.C. J. Am. Chem. Soc. 1968, 90, 6243; (b) Zweifel, G.; Miller, R.L. Ibid. 1970, 92, 6678.

^{660.} Yamamoto, Y.; Yatagai, H.; Maruyama, K. J. Org. Chem. 1980, 45, 195.

^{661.} Amarasinghe, K.K.D.; Montgomery, J. J. Am. Chem. Soc. 2002, 124, 9366.

^{662.} Hoye, R.C.; Baigorria, A.S.; Danielson, M.E.; Pragman, A.A.; Rajapakse, H.A. J. Org. Chem. 1999, 64, 2450.

^{663. (}a) Strohmeier, W. Chem. Ber. 1961, 94, 2490; (b) Rausch, M.D. J. Org. Chem. 1974, 39, 1787.

^{664.} Semmelhack, M.F.; Bisaha, J.; Czarny, M. J. Am. Chem. Soc. 1979, 101, 768.





Arylchromium complex **759** reacts with carbon nucleophiles via nucleophilic aromatic substitution. As shown in Table 8.23,⁶⁶⁵ organolithium reagents and enolates add to **759** to generate a carbanionic complex **762**. The nucleophilic addition can be reversible if complex **762** is heated. The complex can be decomposed by reaction with iodine (to give **763**) or by protonolysis (with trifluoroacetic acid, TFA) to give cyclohexadiene derivative **764**. The reagents used to remove the metal are similar to those used with organoiron complexes (sec. 8.9.A).

Table 8.23.Nucleophilic Aromatic Substitution of 759 by Organolithium Reagents and
Enolate Anions



When the benzene ring is functionalized, the chromium complex can react with nucleophiles to

665. (a) Semmelhack, M.F.; Hall, H.T.; Yoshifuji, M.; Clark, G. J. Am. Chem. Soc. 1975, 97, 1247; (b) Semmelhack, M.F.; Hall, Jr., H.T.; Yoshifuji, M. Ibid. 1976, 98, 6387.
give ortho, meta or para isomers. In general, the meta substitution product predominates^{666,667} but all three isomeric products are formed. These transformations have been used in synthesis. Semmelhack and co-workers,^{668,666} used an arylchromium complex in a synthesis of acorenoneand also in a synthesis of (\pm)-frenolicin that exploited the lithium-hydrogen exchange reaction.⁶⁶⁹ Chromium complexes of polynuclear aromatic molecules undergo nucleophilic substitution, but not on the ring complexed to chromium.⁶⁷⁰ Asymmetric induction is possible when chiral ligands are used in conjunction with the organolithium addition reactions. The reaction of **765** with phenyllithium in toluene, in the presence of (–)-sparteine gave complex **766**, which was treated with propargyl bromide to give a 72% yield of **767** in 54% ee.⁶⁷¹



A different asymmetric application allows formation of CH₂Li units from *ortho*-methyl groups in chromium-arene complexes, which then react as carbon nucleophiles. Amide **768** reacted with butyllithium⁶⁷² in the presence of a chiral amine, and subsequent reaction with benzyl bromide gave **769** in 63% yield and 67% ee. The amide unit clearly activates the substituent at *ortho*-position to substitution, and the presence of the chiral amine led to asymmetric induction.



The disconnections available from these organochromium reactions are:



- 666. Semmelhack, M.F.; Harrison, J.J.; Thebtaranonth, Y. J. Org. Chem. 1979, 44, 3275.
- 667. (a) Semmelhack, M.F.; Clark, G.R.; Farina, R.; Saeman, M. J. Am. Chem. Soc. 1979, 101, 217; (b) Semmelhack, M.F.; Hall, Jr., H.T.; Farina, R.; Yoshifuji, M.; Clark, G.; Bargar, T.; Hirotsu, K.; Clardy, J. Ibid. 1979, 101, 3535.
- 668. Semmelhack, M.F.; Yamashita, A. J. Am. Chem. Soc. 1980, 102, 5924
- 669. Semmelhack, M.F.; Zask, A. J. Am. Chem. Soc. 1983, 105, 2034.
- 670. Semmelhack, M.F.; Seufert, W.; Keller, L. J. Am. Chem. Soc. 1980, 102, 6584.
- 671. Amurrio, D.; Khan, K.; Kündig, E.P. J. Org. Chem. 1996, 61, 2258.
- 672. Koide, H.; Hata, T.; Uemura, M. J. Org. Chem. 2002, 67, 1929.

In general, nucleophilic aromatic substitution reactions are rather difficult with unsubstituted aryl derivatives, or when the aromatic ring contains a strongly electron-releasing group. Formation of the chromium complex activates such aromatic compounds to nucleophilic substitution. Since the nucleophiles are carbon nucleophiles, this technique offers a route to carbon bonds that would be very difficult to form by other methods.

8.10. ALLYLIC TIN, ALKYLTITANIUM, AND ALLYLIC SILANE COMPLEXES

Other metal derivatives can be used for coupling. Among the more popular reagents are allylor alkyl-metallic compounds of tin and titanium. Allylsilanes can also be used if a Lewis acid is added.

8.10.A. Allyltin Reagents

OR 770	CHO $\xrightarrow{\text{Sn}(n-\text{Bu})_3}$ Lewis acid	OR OH 771	+	OR
R	Lewis Acid	<u>Solvent</u>	<u>Temp. (°C)</u>	<u>771 : 772</u>
CH ₂ Ph	BF ₃ •OEt ₂	CH_2Cl_2	-78	39:61
	MgBr ₂	ether THF CH ₂ Cl ₂	-23	94 : 6 20 : 80 >250 : 1
	MgCl ₂	ether THF CH ₂ Cl ₂		no reaction 22 : 78 no reaction
	Mg(ClO ₄) ₂	ether		69:31
	ZnBr ₂	THF CH ₂ Cl ₂ PhMe	67	27 : 73 77 : 23 41 : 59
	ZnI_2	ether CH ₂ Cl ₂		35 : 64 97 : 3
	TiCl ₄	CH_2Cl_2	-78	>250:1
SiMe ₂ t-Bu	TiCl ₄ MgBr ₂ ZnL	CH ₂ Cl ₂ CH ₂ Cl ₂	-78	36 : 64 21 : 79 53 : 47
	BE ₂ •OEt ₂	CH ₂ Cl ₂	-78	9 · 91
	$BF_3 \cdot OEt_2$ (2 equiv)	CH_2Cl_2 CH_2Cl_2	-78	5 : 95
[Reprinted with permission from Els	nission from Keck, G.E.; Bode evier Science.]	n, E.P. Tetrahedron	Lett. 1984, 25, 265, Cop	pyright 1984 , with

 Table 8.24.
 Condensation of Allyltributyl Stannane with Chiral Aldehydes (770)

Tetravalent tin complexes add to aldehydes and ketones in the presence of a Lewis acid. Allyltin complexes are, by far, the most widely used of these compounds.⁶⁷³ A typical example

673. For reactions of this type, see Larock, R.C. Conmprehensive Organic Transformations, 2nd ed., Wiley-VCH, New York, 1999, pp 373-378.

is taken from the work of Keck and Boden, in which a chiral aldehyde (770) was treated with allyltributyltin and various Lewis acids.⁶⁷⁴ As shown in Table 8.24,⁶⁷⁴ a mixture of syn (771) and anti (772) products was obtained. The ratio of 771/772 was dependent on the structure of the R group in 770, the solvent and the Lewis acid.⁶⁷⁴ The anti product (772) was obtained by using the *tert*-butyldimethylsilyloxy derivative (sec. 7.3.A.i) of 770 with two equivalents of boron trifluoride in dichloromethane. The syn product is obtained preferentially when the benzyloxy derivative of 770 is used with titanium tetrachloride in dichloromethane.⁶⁷⁴

Allyltin and crotyltin coupling is highly diastereoselective. In a synthesis of (+)-roxaticin, Evans and Connell reacted aldehyde **773** with allyltributytin in the presence of SnCl₄, and obtained a 90% yield of **774** with a 35:1 diastereoselectivity.⁶⁷⁵ As the size of the group attached to the α -carbon of the aldehyde increased, the diastereoface selectivity increased for the syn diastereomer relative to allyltin compounds. In the example cited, the chelation product exceeded the product predicted by the Felkin-Anh model (sec. 4.7.B), being formed in a ratio of >200:1. In general, the Felkin-Anh model (predicting the syn diastereomer) gave the greatest success when BF₃ was used as a catalyst in the presence of diphenyl-*tert*-butylsilyloxy aldehydes.⁶⁷⁶ Chelation control with silyloxy derivatives did not contribute significantly to any condensation product,^{676a} although MgBr₂ gave 91:9 diastereofacial selectivity and 89:11 syn selectivity.^{676a} Enantioselective addition of allyltributytin to aldehydes is also possible, using Ti(O*i*-Pr)₄ and a chiral binaphthol derivative such as (*S*)-BINOL [(*S*)-(-)-1,1'-bi-2-naphthol]. In a synthesis of mucocin, Takahashi and co-workers reacted aldehyde **776** (>98% ee).



When benzaldehyde reacted with HO 2-methylbut-3-en-1-ol,⁶⁷⁸ a 78% yield of Me 777 was obtained as a 49/1 (*E/Z*) mixture.



^{674.} Keck, G.E.; Boden, E.P. *Tetrahedron Lett.* **1984**, 25, 265. Allyltributyl tin can undergo conjugate addition, as in a synthesis of *ent*-Sch 47554 by Morton, G.E.; Barrett, A.G.M. *Org. Lett.* **2006**, *8*, 2859.

^{675.} Evans, D.A.; Connell, C.T. J. Am. Chem. Soc. 2003, 125, 10899.

^{676. (}a) Keck, G.E.; Abbott, D.E. *Tetrahedron Lett.* 1984, 1883; (b) Keck, G.E.; Abbott, D.E.; Boden, E.P.; Enholm, E.J. *Ibid.* 1984, 25, 3927.

^{677.} Takahashi, S.; Kubota, A.; Nakata, T. Angew. Chem. Int. Ed. 2002, 41, 4751.

^{678.} Sumida, S.-i.; Ohga, M.; Mitani, J.; Nokami, J. J. Am. Chem. Soc. 2000, 122, 1310.

Tin-catalyzed addition of the alcohol substrate to the aldehyde, followed by a [3,3]-sigmatropic rearrangement, led to the products. Clearly, this is not the same reaction, but it is useful to compare it with the other reactions.

The allyltin disconnections are

$$R \swarrow K + R - X^{1} \qquad Ph \stackrel{R}{\longrightarrow} Ph - X + X^{1} \stackrel{R}{\longrightarrow} R^{1} \stackrel{OH}{\longleftarrow} R^{1} \stackrel{CHO}{\longleftarrow} R^{1} \stackrel{R^{2}_{3}Sn}{\underset{R}{\longrightarrow}} R^{1} \stackrel{CHO}{\longrightarrow} R^{1} \stackrel{R^{2}_{3}Sn}{\underset{R}{\longrightarrow}} R^{1} \stackrel$$

Other allyl metal complexes can be used to generate carbon bonds, including allyl zinc complexes. Stille showed that 3-methyl-1-bromo-2-butene reacted with zinc chloride (ZnCl₂) to generate the π -allyl zinc species. Coupling required the use of an organotin species such as α -trimethyltin isoprene (**778**). Reaction in refluxing THF led to a 94% yield of myrcene (**779**).⁶⁷⁸



8.10.B. Alkyltitanium Reagents

A related coupling reaction is the condensation of aldehydes with alkyl trichlorotitanium compounds (RTiCl₃). When methyltrichlorotitanium (MeTiCl₃) was coupled with aldehyde **780** in dichloromethane at -78° C, a 91:9 mixture of **782**/**783** was formed via the chelated complex **781**.⁶⁷⁹ Allyltitanium compounds also couple to aldehydes. In a synthesis of FR66979,⁶⁸⁰ Cuifolini and Ducray reacted aldehyde **784** with allyltitanium anion **785** and obtained alcohol **786** in good yield.



679. Reetz, M.T.; Jung, A. J. Am. Chem. Soc. 1983, 105, 4833.

680. Ducray, R.; Ciufolini, M.A. Angew. Chem. Int. Ed. 2002, 41, 4688.

8.10.C. AllyIsilane Reagents

Another variation of this reaction couples an aldehyde with an allylsilane (rather than an allyltitanium species), in the presence of a Lewis acid. Sakurai and Hosomi had previously noted the coupling of allylsilanes to aldehydes in the presence of $TiCl_{4}$.⁶⁸¹ Reetz et al. used $TiCl_{4}$, $SnCl_{4}$, BF_3 or AlCl_3 in reactions of allyltrimethylsilane, and observed good diastereoselectivity.⁶⁸² In this study, the solubility of the Lewis acid, and the temperature of the reaction the Lewis acid employed were important factors for both reactivity and selectivity. A high degree of stereoselectivity is possible, if a chiral catalyst is used. In a synthesis of fostriecin,⁶⁸³ Shibasaki and co-workers reacted conjugated aldehyde **787** with allyltrimethoxysilane in the presence of AgF and (*R*)-*p*-tolyl-BINAP, and obtained an 80% yield of **788** (dr = 28:1).



Heathcock and Kiyooka examined a similar coupling with aldehydes having a stereogenic α -carbon (as in **789**) rather than the β -carbon (as in Reetz's **787**). Upon reaction with allyltrimethylsilane, aldehyde **789** gave a mixture of **790** and **791**.⁶⁸⁴ Using tin tetrachloride (SnCl₄) as a catalyst provided better syn selectivity in the products (**790** and **791**) than did BF₃



or $TiCl_4$ ($TiCl_4$ did not catalyze this coupling reaction).⁶⁸⁴ As with the allyltin complexes, these results are explained by chelation control. A synthetic example, taken from Fürstner and co-

worker's synthesis of herbarumin I, also illustrates an interesting variation.⁶⁸⁵ Furanose derivative **792** reacted with allyltrimethylsilane in the presence of TMSOTf to give **793** (58% of the β -anomer + 5% of



^{681. (}a) Hosomi, A.; Sakurai, M. Tetrahedron Lett. 1976, 1295; also see (b) Trost, B.M.; Coppola, B.P. J. Am. Chem. Soc. 1982, 104, 6879.

^{682.} Reetz, M.T.; Kesseler, K.; Jung, A. Tetrahedron Lett. 1984, 25, 729.

^{683.} Fujii, K.; Maki, K.; Kanai, M.; Shibasaki, M. Org. Lett. 2003, 5, 733.

^{684. (}a) Kiyooka, S.; Heathcock, C.H. *Tetrahedron Lett.* 1983, 24, 4765; (b) Heathcock, C.H.; Kiyooka, S.; Blumenkopf, T.A. J. Org. Chem. 1984, 49, 4214.

^{685.} Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C.W.; Mynott, R. J. Am. Chem. Soc. 2002, 124, 7061.

the α -anomer). The allylsilane reacted via the aldehyde generated *in situ* from the protected hemi-acetal.

8.10.D. Silane Carbanions

Allylic silanes are synthetically useful compounds⁶⁸⁶ that are usually prepared by reaction of chlorotrialkylsilanes and allylic Grignard reagents, as with the preparation of the *tert*-butyldimethylsilane **796**.⁶⁸⁷ When a silane such as **794** is treated with fluoride ion, fluoride attacks the silicon and displaces the carbanion **795**. If the anion is generated in the presence of an electrophile, typical carbanion reactions occur. It is unlikely that the carbanion (**795**) has a significant lifetime as a discrete entity. Indeed, it need not exist at all, since the carbanionic character of that carbon increases as the fluoride departs, forming a transient hypervalent silicon species. Sakurai showed that allylic silanes react with ketones or aldehydes and tetra-*n*-butylammonium fluoride (TBAF) in THF. Allyl silane **797** reacted with butanal in the presence of TBAF⁶⁸⁸ to give an 83% yield of alcohol **798**. Similar reaction of allylic silanes with TBAF, in the presence of benzophenone gave the acyl substitution product.⁶⁸⁸



The disconnection for silane carbanion addition to carbonyls is



Majetich and co-workers showed that fluoride-generated carbanions undergo Michael-type additions.⁶⁸⁹ To achieve conjugate addition with carbanions generated from silanes usually requires the use of DMF as a solvent, and HMPA is often added to obtain satisfactory yields. In this example, **799** was treated with TBAF to generate the carbanion **800**. Intramolecular Michael addition and hydrolysis led to the bicyclic product **801**.⁶⁸⁹

^{686.} Chabaud, L.; James, P.; Landais, Y. Eur. J. Org. Chem. 2004, 3173

^{687.} Hosomi, A.; Sakurai, H. Tetrahedron Lett. 1978, 2589.

^{688. (}a) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043; (b) Sakurai, H. *Pure Appl. Chem.* **1982**, 54, 1.

 ^{689. (}a) Majetich, G.; Desmond, Jr., R.W.; Soria, J.J. J. Org. Chem. 1986, 51, 1753; (b) Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. Ibid. 1986, 51, 1745.



Note that Vedejs used the fluoride/silane carbanion reaction to generate a novel imidate ylid that was used in a [3+2]-cycloaddition reaction with ethyl acrylate (sec. 11.11.F).⁶⁹⁰

The disconnections possible with these latter reactions are



8.11. PHENOLIC CARBANIONS

There are additional methods for generating carbanionic centers that are not classified in previous sections. Two of the more useful are treatment of organosilanes with fluoride and formation of resonance stabilized aromatic carbanions. These two methods will be presented in this section, with an emphasis on the more synthetically useful versions of each reaction.

When phenols are treated with base, the resulting phenoxide ion (802) has four resonance contributors as shown. If an electrophilic species were added to 802, the major product is usually



the ether (*O*-alkylation) via Williamson ether synthesis (sec. 2.6.A.i). If an electrophilic center is tethered to the phenolic moiety, however, it is possible to trap the carbanion center intramolecularly. Winstein showed that *p*-bromophenylsulfonyl (OBs) derivatives such as **803** reacted with potassium *tert*-butoxide to give the reactive carbanion intemediate **804**.⁶⁹¹ In the absence of an exogenous electrophile, carbanionic resonance contributors can displace an attached leaving group such as bromine, iodine, or a sulfonate ester to form a carbocyclic ring. When **803** was treated with *tert*-butoxide, **804** is one resonance contributor of the intermediate. Displacement of the bromobenzenesulfonyl leaving group in **804** by the aromatic carbanion

^{690. (}a) Vedejs, E.; Larsen, S.; West, F.G. J. Org. Chem. **1985**, 50, 2170; (b) Vedejs, E.; Martinez, G.R. J. Am. Chem. Soc. **1979**, 101, 6452; **1980**, 102, 7993; (c) Vedejs, E.; West, F.G. J. Org. Chem. **1983**, 48, 4773.

^{691.} Baird, R.; Winstein, S. J. Am. Chem. Soc. 1962, 84, 788.

proceeded via an Ar_1^{-5} mechanism⁶⁹² to give the spirocyclic ketone (805).



A phenol need not be used directly, as long as a phenoxide anion can be formed easily. Spirocyclization of a bis(methanesulfonate) has been reported, where the requisite phenolic anion is generated *in situ*.⁶⁹³ Corey and co-workers⁶⁹⁴ as well as Crandall and Lawton⁶⁹⁵ used spirocyclization to construct the spirocyclic portion of cedrene. In another example, phenol derivative **806** was treated with potassium *tert*-butoxide to give a 73% yield of **807** in Mukherjee and co-workers synthesis of zizaene.⁶⁹⁶ In another example, Fukuyama and co-workers⁶⁹⁷ converted **808** to **809** (77% yield) in a synthesis of duocarmycin.



This spirocyclic disconnection is



^{692. (}a) Winstein, S.; Heck, R.; Lapporte, S.; Baird, R. *Experientia* 1956, 12, 138; (b) Heck, R.; Winstein, S. J. Am. Chem. Soc. 1957, 79, 3105; (c) Winstein, S.; Baird, R. *Ibid.* 1957, 79, 756; (d) Scott, F.L.; Glick, R.E.; Winstein, S. *Experientia* 1957, 13, 183.

- 695. Crandall, T.G.; Lawton, R.G. J. Am. Chem. Soc. 1969, 91, 2127.
- 696. Pati, L.C.; Roy, A.; Mukherjee, D. Tetrahedron 2002, 58, 1773.
- 697. Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. J. Am. Chem. Soc. 2003, 125, 6630.

^{693.} Marx, J.N.; Bih, Q.-R. J. Org. Chem. 1987, 52, 336.

^{694.} Corey, E.J.; Girotra, N.N.; Mathew, C.T. J. Am. Chem. Soc. 1969, 91, 1557.

8.12. CONCLUSION

This chapter has shown how incorporation of a metal or an appropriate electron withdrawing group or atom gives carbanions that can be used to form new carbon-carbon bonds. The great variety of nucleophilic species, the range of electrophilic species with which they react, and the high degree of stereoselectivity which accompanies many of the reactions show why these are among the most powerful disconnections in organic synthesis. The useful carbonyl stabilized carbanions, the enolates will be discussed in Chapter 9.

HOMEWORK

1. Predict the major product and explain the stereochemistry of the following reaction.



2. The Grignard reaction of compound **86** in the text gave alcohol **87**. Offer an explanation for this selectivity.



3. Given the reaction sequence, give a mechanistic rationale for formation of the cyclohexanone product.

HO
SPh
$$1. \text{ KH, THF/HMPA, -11 } +25^{\circ}\text{C}$$
 PhS 0

4. In each case, draw the transition state for the Cram, Karabatsos and Felkin-Anh models of the reaction of each molecule with (1) MeMgBr (2) PhMgCl (3) CH₃C=C:⁻Na⁺ (4) EtLi (5) 2-lithio-1,3-dithiane.



Draw the major product(s) that result from each reaction, after hydrolysis.

5. The following reaction gives a diastereomeric ratio of about 3:1. Draw both of these products, and predict the major product.

OHC
$$- \underbrace{ \begin{array}{c} O \\ O \\ C \end{array} }_{Et} \underbrace{ \begin{array}{c} BuLi \\ BuLi \end{array} }_{Et}$$

6. Give a mechanistic explanation for the formation of the product shown from the designated starting material.



7. Give the major product for (a-e) when treated with (1) *n*-BuLi/THF/-78°C; (2) MeI/-78 $\rightarrow 0^{\circ}$ C; (3) aq NH₄Cl.

(a)
$$\langle O \rangle$$
 (b) $\langle S \rangle$ (c) $\langle N \rangle$ (d) $\langle O \rangle$ C=C-H (e) $\langle SPh \rangle$

8. For each of the following give a complete reaction that illustrates its use for the formation of a carbon-carbon bond:

(a) CdCl₂; (b) Cp₂TiMe₂; (c) CeCl₃ (d) lithium 2,2,6,6-tetremethylpiperidide; (e) CO; (f) CuCN; (g) *N*,*N*,*N*',*N*'-tetramethylethylenediamine; (h) FeCl₃; (i) NaCN; (j) NaNH₂; (k) BF₃; (l) Na₂Fe(CO)₄; (m) *i*-Bu₂AlH; (n) PPh₃; (o) NaH; (p) (MeO)₂POMe; (q) DMSO.

9. Rationalize formation of the indicated product in this reaction.



10. Each of the following molecules can be used to standardize a solution of an organolithium reagent. Describe, with reactions, the acid-base chemistry involved in each reaction.



11. Provide a suitable synthetic sequence for each transformation (a-d).



12. For (a-c) give the major product of each reaction, with correct stereochemistry, and justify your choice.



13. In each of the following reactions, predict the major product, with the correct stereochemistry where appropriate:





chapter 8 777



14. Provide a synthesis for each of the following transformations. Show all reagents and intermediate products.





15. Synthesize each of the following molecules from a starting material of no more than six carbons. That starting material must be commercially available from a chemical company. Show your retrosynthetic analysis and all reagents and intermediate products of the synthesis.



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C^d Disconnect Products: Nucleophilic Species that Form Carbon-Carbon Bonds: Enolate Anions

9.1. INTRODUCTION

9

chapter

In Chapter 8, a hydrogen atom on a carbon α to an electron-withdrawing group was shown to be a weak acid. Removal of that proton by a base generated several synthetically useful reagents that contained a carbanion center, and functioned as a C^d disconnect product (sec. 1.2). When the electron-withdrawing group is a single carbonyl group (ketones, aldehydes, esters, etc.), the pK_a of the adjacent protons are generally in the range pK_a 19-24.¹ As discussed in Section 8.5.G, the effects of the carbonyl group are due to (1) the inductive electron-withdrawing ability of the unsaturated substituent, but mainly due to (2) the ability of these substituents to delocalize the negative charge remaining after a proton has been removed.² With the enhancement in acidity induced by the carbonyl, weaker bases can be used for deprotonation when compared to sulfides, sulfoxides and so on (introduced in Chapter 8).² Deprotonation generates a resonance stabilized **enolate anion**. The bases used in previous chapters are all rather nucleophilic, and when dealing with aldehydes, ketones or carboxylic acid derivatives, acyl addition to the carbonyl may compete with deprotonation. Acyl addition must be suppressed or diminished if an enolate anion is to be generated, and used in subsequent reactions. This result can be achieved by decreasing the nucleophilicity of the base while maintaining or enhancing its basicity. This chapter will introduce enolate anions, and discuss solutions to the problems posed, as well as synthetically useful reactions.

9.2. FORMATION OF ENOLATE ANIONS

9.2.A. Preparation and Properties

The attachment of an electron-withdrawing carbonyl on a C–H moiety enhances the acidity of that hydrogen, the so-called α -hydrogen. Reaction of a carbonyl derivative such as 3-methyl-2-butanone (1) and a suitable base leads to an acid-base reaction in which H_a is removed (as H⁺), making the α -carbon a carbanion (see 2). This carbanion (called an **enolate anion**)

^{1.} House, H.O. *Modern Synthetic Reactions, 2nd Ed.*, W.A. Benjamin, Menlo Park, CA., **1972**, p 494 and references 1, 2b cited therein.

 ⁽a) d'Angelo, J. Tetrahedron 1976, 32, 2979; (b) Stowell, J.C. Carbanions in Organic Synthesis Wiley-Interscience, New York, 1979, pp 127-216.

is resonance stabilized, with the electrons delocalized on the carbon and on the oxygen. If the carbanion center is the preferred site for reaction, an enolate anion will behave like any other nucleophilic center upon reaction with an electrophile, so an enolate anion is a carbon nucleophile. Table 9.1 reproduces a portion of Table 8.16 in Section 8.5.H, and several things are apparent. In 1, there are two chemically different types of α -hydrogen atoms (H_a and H_b). There are three identical hydrogen atoms on the methyl group (labeled H_b), and one on C3 (labeled H_a). The presence of the electron-releasing methyl groups on the α -carbon diminishes the acidity of H_a because the C–H_a bond is less polarized.



Table 9.1. pK_a values of Typical Carbon Acids

Carbon Acid	<u>pKa</u>	<u>Carbon Acid</u>	p <u>K</u> a	Carbon Acid	<u>pKa</u>	Carbon Acid	<u>pK</u> a
N≡C → ^H	25 ^a	$\underbrace{\begin{array}{c} CO_2Et\\ H\\ CO_2Et\end{array}}_{CO_2Et}$	15 ^a	γ_{4}^{0} H	20.8 ^{b,c}	O Cl H	16.5 ^a
о НО [№] <u>Ш</u>	24 ^a	H Me O Me	11 ^a		23.5 ^{b,c}	$\mathbf{H} \stackrel{\mathrm{CO}_2\mathrm{Et}}{\underset{\mathrm{CO}_2\mathrm{Et}}{\leftarrow}}$	13.3 ^a
→ → 5	21.3 ^b	7 CHO H≺CHO 9	5.9 ^a	О Н З	20 ^a		9.0 ^a
Ph H	19.5 ^b	$\mathbf{H}\overset{\mathrm{NO}_2}{\underset{\mathrm{NO}_2}{\leftarrow}}$	3.6 ^a	о _{Рh}	19.1 ^{d,b}	$MeO_2S \xrightarrow{O} Me$	4.7 ^a
Ph H	18.6 ^b					10.0	

a Ref. ³ b ref. ⁴, c Ref. ⁵ d Ref. ⁶

This trend can be seen in Table 9.1 by comparing **3** (acetone) with **4** that has a pK_a of 20.8. They are obviously close. However, when **4** is compared to **5**, with a pK_a of 21.3, and **6** with a pK_a of 23.5, the presence of the alkyl substituents leads to a higher pK_a (less acidic proton). Since deprotonation is an acid-base reaction, and we know that alkyl groups are electron-releasing, the effect on the equilibrium is that the carbanionic center in the enolate anion is

^{3.} Pearson, R.G.; Dillon, R.C. J. Am. Chem. Soc. 1953, 75, 2439.

^{4.} Zook, H.D.; Kelly, W.L.; Posey, I.Y. J. Org. Chem. 1968, 33, 3477.

^{5.} Reference 1, p 494.

^{6.} Cram, D.J. Fundamentals of Carbanion Chemistry, Academic Press, New York, 1965, pp 4, 10, 13, 14, 43, 48.

destabilized and the C–H_a bond is stronger (see 1). These factors shift the acid-base equilibrium to the left (toward 1) and contribute to decreasing acidity of the hydrogen. The α -hydrogen of an aldehyde is more acidic than that of a ketone, as seen by comparing malonaldehyde (9, pK_a of 5.9) with acetylacetone (8, pK_a of 9.0). Comparing the α -hydrogen of acetone to the α -hydrogen of acetic acid (pK_a of 20 versus 24) shows that the α -hydrogen of the ketone is more acidic. If acetone is compared with acetylacetone (8, pK_a of 9.07 in Table 9.1) it is clear the presence of the second carbonyl group greatly enhances the acidity of H_a. The presence of an electron-releasing methyl group in 7 diminishes the acidity (pK_a of 11). An electron withdrawing sulfonyl group (see 10) enhances the acidity (pK_a of 3.6).

The enol content of carbonyl derivatives correlates with the acidity of the α proton. In ketone **11** the acidic proton of the enol (**12**) is attached to oxygen rather than carbon (from the keto form, **11**). Removal of H_a from **12** generates enolate anion **13**. Removal of H_a from **11** simply generates the other resonance contributor. In general, monoalkylated ketone derivatives such as **11** exist primarily in this keto form, but 1,3-dicarbonyl derivatives (such as **7-10** for example) have relatively high concentrations of enol (see **12**), and this contributes to the greater acidity of the proton on the α -carbon. The relative enol content of a molecule is strongly dependent on the solvent, as observed with ethyl acetoacetate.⁷ For ethyl acetoacetate, the enol content is 0.4% in water, 2.2% in 50% aqueous ethanol, 6.9% neat, 11% in ethanol, 27% in ether, and 46% in hexane.⁷ There is a clear dependence on hydrogen-bonding ability and polarity. The extensive hydrogen bonding that is possible in water minimizes intramolecular stabilization of the enol, whereas aprotic solvents such as ether or hexane maximize the intramolecular hydrogen bonding, which stabilizes the enol. Removal of a proton connected to oxygen is expected to be more facile than similar removal from a carbon, and one expects that as the enol content increases, the acidity should increase.



MOLECULAR MODELING: Hydrogen Bonding and Keto-Enol Tautomerism

It is known that propanal exists almost exclusively as the keto form, whereas there is evidence to suggest that *cis*-3-hydroxyacrolein (the enol form) is actually more stable than its keto form, malonaldehyde $(CH_2-(CHO)_2, A)$.



^{7.} Stewart, R. The Investigation of Organic Compounds, Prentice-Hall, Englewood Cliffs, NJ, 1966, p.12.

MOLECULAR MODELING: Hydrogen Bonding and Keto-Enol Tautomerism, con't.

Obtain the energy for the conformer of malonaldehyde in which one of the CO double bonds eclipses a CC single bond and the other CO bond eclipses a CH bond. This is actually the lowest-energy conformer. *Click* on > at the right of the tab at the top of the screen and select *Continue* to bring up a fresh builder pallet. Obtain the energy for the s-*cis* conformer *cis*-3-hydroxyacrolein (the enol form) in which the OH hydrogen atom is pointed toward the carbonyl group (the conformer shown above). Which is favored, the keto or enol? Provide an explanation to your result. Hint: What is the energy of the s-*trans* conformer *cis*-3-hydroxyacrolein?

There is a clear correlation between enhanced acidity of a ketone or aldehyde and increased enol content, but inductive effects also play a role in the increased acidity of H_a for 1,3-dicarbonyl derivatives such as **11** (where $R^1 = CO_2Et$; sec. 2.2.A). The carbonyl group is a typical electron-withdrawing substituent but there are many others. In chapter 8, the ability to increase the acidity of a proton was shown to follow the order:

$NO_2 > O_1 = SO_2R > C$	$O_{\text{II}} \approx C = N > C \sim OR$	O II > Ph $C \sim R$
	01	K

and this is reflected in Table 9.1. Note that recent studies of X-ray structures of enolate anions and amide bases suggest that the enolate anion may be formed by direct removal of the proton from the α -carbon via an intermediate tetrameric lithium complex involving the base and the carbonyl starting material (sec. 9.2.D). Whether the α -hydrogen is removed directly from carbon or from the O–H of an enol, the presence of an electron-withdrawing group enhances the acidity of that hydrogen. The presence of two or more groups enhances the acidity of an α -proton even more, but the effect is not strictly additive, as shown in Table 9.2.^{8,3}

Table 9.2. Enhancement of Acidity with Increasing Number of Electron-Withdrawing Groups

Compound	<u>pKa</u>	Compound	pK _a			
CH ₃ NO ₂	11	CH ₃ COCH ₃	20			
$CH_2(NO_2)_2$	4	CH ₂ (COCH ₃) ₂	9			
CH(NO ₂) ₃	0	CH(COCH ₃) ₃	6			
CH ₃ SO ₂ CH ₃	23	CH ₃ CN	25			
$CH_2(SO_2CH_3)_2$	14	$CH_2(CN)_2$	12			
CH(SO ₂ CH ₃) ₃	0	CH(CN) ₃	0			
[Reprinted with permission from Pearson, R.G.; Dillon, R.C. J. Am. Chem. Soc. 1953, 75, 2439. Copyright © 1953 American Chemical Society.]						

^{8. (}a) Buncel, E. *Carbanions: Mechanistic and Isotopic Aspects*, Elsevier, Amsterdam, **1975**, p 5; (b) Reference 6, p. 12.

MOLECULAR MODELING: Electrostatic Potential Maps and Relative CH Acidities

The electrostatic potential is the energy of interaction of a point positive charge with the nuclei and electrons that make up a molecule. As such, it provides a broad indicator of excess positive or negative charge at any location. A more useful indicator, termed an electrostatic potential map, is provided by coloring different locations on an electron density surface (designating overall molecular size and shape) with the value of the electrostatic potential. By convention, locations with excess positive charge are colored "blue", while those with excess negative charge are colored "red". Neutral regions are colored "green".

Electrostatic potential maps may be used to rank the acidities of closely-related compounds, for example, the CH acidities of alkanes (substituted methanes). It is known that replacing H with an electron-withdrawing group such and CN or NO₂ leads to significant increase in the acidity of the hydrogen atoms remaining on that carbon. In other words, nitromethane is more acidic than methane. One after another, obtain geometries and electrostatic potential maps for acetonitrile, malonitrile and tricyanoethylene. Start the second and third calculations by *clicking* on > at the right of the tab at the top of the screen and selecting **Continue**. Compare the three maps, focusing on the region around the acidic hydrogen(s). The more positive ("blue") the electrostatic potential in this region, the more acidic the hydrogen (and the compound). You can switch between transparent displays, allowing you to see the structures underneath, and solid displays, allowing easier comparisons, *clicking* on the map and selecting either *Transparent* or *Solid* from the **Style** menu at the bottom of the screen. Which compound is the most acidic and which is the least acidic?

Repeat your calculations and analysis for nitromethane, dinitromethane and trinitromethane. Is the ordering of acidities with increasing number of electron-withdrawing groups the same as noted for the cyano compounds? Is the nitro group more or less effective in increasing CH acidity? Elaborate.

MOLECULAR MODELING: Site of Protonation in Pyrrole and Indole

Quantum chemical models may be used to compare base strengths (measured as their proton affinities) of related molecules. Such models may also be used to identify the most basic site within a given molecule and to rank the strengths of alternative sites. Such an analysis is important to determine if there may be more than one site for protonation in an acid-base reaction and, if there is, which site is likely to be most basic. Even a molecule as simple as pyrrole offers three different protonation sites: the nitrogen, C_2 and C_3 . Use two different modeling tools to assign which site is favored.

The simpler approach is to examine the electrostatic potential map for pyrrole itself. Build pyrrole and *click* on the electrostatic potential map icon. In turn, *click* on regions of the map in the vicinity of N, C_2 and C_3 to obtain the electrostatic potential (a numerical value is displayed at the bottom of the screen). You might find it helpful to switch from a solid to a transparent model in order to see the underlying structure. *Click* on the map and select *Transparent* from the **Style** menu at the bottom right of the screen. Remember that blue regions indicate electron acceptor sites, such as acidic protons, whereas red regions indicate electron-donating (basic) sites. Based on this analysis, which atom is the most basic, and where does pyrrole protonate?

MOLECULAR MODELING: Site of Protonation in Pyrrole and Indole, con't.

The more complicated but usually more reliable approach to assess relative basicity is to compare the energies of the positive ions resulting from protonation. *Click* on > and select *Continue* from the screen to bring up a fresh build palette. Build N-protonated pyrrole starting from the NH_4^+ icon and obtain its energy. Repeat the process for C_2 and C_3 protonated pyrrole (build each starting from the CH_3^+ icon). Which protonated form is most stable (lowest in energy)? Is it reasonable to expect that two or more different protonated forms of pyrrole will be seen in an equilibrium mixture at room temperature? Elaborate. Is your conclusion the same as that you arrived at by comparing electrostatic potential maps?

Repeat both electrostatic potential map and energy calculations for indole and its protonated forms. Consider only protonation sites that are analogous to those in pyrrole (in the five-membered ring, and not those associated with the benzene ring). Is the preferred protonation site in indole the "same" as it is in pyrrole? Is the ordering of the nitrogen and two carbon proton affinities the same in the two molecules? If not provide an explanation as to why not.

9.2.B. Non-Nucleophilic Bases

Although the carbonyl group enhances the acidity of the α -proton, it also reacts with the base used for the deprotonation via acyl addition. Both organolithium or Grignard reagents are powerful bases, but they react with carbonyl derivatives primarily by nucleophilic acyl addition to the carbonyl, as in the reaction of 3-hexanone and *n*-butyllithium to give **14**. This acyl addition reaction can be suppressed somewhat by lowering the reaction temperature to -78° C, -100° C or even lower, but nucleophilic addition is usually quite facile. Other bases must be used to remove the α -proton in the acid-base reaction.

Ideally, the base would not be very nucleophilic, to suppress acyl addition. However, the base must be sufficiently basic to remove a relatively weak acidic proton.



Hydroxide and alkoxides (formed from reaction of alcohols with NaH, NaOH, etc.) are strong enough bases to deprotonate most ketones. Sodium hydroxide (NaOH) in water or alcohol can be used, as well as MeOH/MeO⁻, EtOH/EtO⁻ or *t*-BuO⁻/*t*-BuOH. These are nucleophilic reagents, however, and their use depends on the reversibility of the nucleophilic addition reaction to allow the deprotonation to compete. The bases NaH and KH are poor nucleophiles and they are very useful for generating enolates, although not kinetically active enough for a wide range of applications. Sodium and potassium hydride are used most often with malonate derivatives, acetoacetic esters, or 1,3-diketones.

Amines are weak acids, and are deprotonated only in the presence of a strong base. When a secondary amine is treated with a strong base, a strong conjugate base ($R_2NH + base \rightarrow R_2N^-M^+$) is generated, the amide anion (R_2N^-). This conjugate base is more basic than the

alkoxide obtained from similar reaction with an alcohol, and is easily capable of removing the α -proton of a ketone or aldehyde. Generation of NaNH₂ from ammonia is well known, and reaction of a secondary amine with a basic molecule such as *n*-butyllithium gives the analogous lithium dialkylamide. Lithium diisopropylamide (**15**,

LDA)⁹ is formed by reaction of diisopropylamine (re, LDA)⁹ is formed by reaction of diisopropylamine and n-butyllithium.¹⁰ At first glance, it appears that LDA has a nucleophilic nitrogen atom. In reactions with carbonyl derivatives, however, nucleophilic attack at the acyl



carbon is sterically blocked. This is illustrated in Figure 9.1, which represents the approach of LDA from the top face to 2-butanone, with the carbonyl oxygen projected to the front.



Figure 9.1. Steric hindrance that inhibits nucleophilic acyl addition of LDA (*top*) as it approaches 2-butanone (*bottom*). The N–Li is aligned with the C=O unit in the front of the diagram.

As the nitrogen approaches the carbonyl group at the required Bürgi-Dunitz angle of about $110^{\circ 11}$ (sec. 6.6.A), the methyl groups of the isopropyl units are repelled by the methyl and ethyl groups, which inhibits nucleophilic attack by nitrogen at the carbonyl carbon. In other words, steric hindrance prevents close contact of the nitrogen and the acyl carbon. Therefore, nitrogen is categorized as a poor nucleophile in this reaction. Since approach to an α hydrogen is not sterically encumbered, LDA reacts as a base without any problem. Dialkylamide bases such as LDA do not react well via acyl addition due to steric hindrance but deprotonate

ketones or aldehydes, so dialkylamides are categorized as **nonnucleophilic bases**. All this really means is that nucleophilic acyl addition is slow relative to the acid-base reaction that removes the α -proton. Virtually any secondary amine can be converted to the corresponding amide base (R₂NLi), including lithium diethylamide (16), lithium tetramethylpiperidide



^{9.} Hamell, M.; Levine, R. J. Org. Chem. 1950, 15, 162.

^{10. (}a) Albarella, J.P. J. Org. Chem. 1977, 42, 2009; (b) Sasson, I.; Labovitz, J. Ibid. 1975, 40, 3670.

^{11. (}a) Bürgi, H.-B.; Shefter, E.; Dunitz, J.D. *Tetrahedron* 1975, 31, 3089. Also see (b) Polt, R.; Seebach, D. J. *Am. Chem. Soc.* 1989, 110, 2622.



 $(17)^{12}$ or lithium hexamethyldisilazide (18),^{13,14} although 15 is probably the most commonly used amide base. In 17, the four methyls at C2 and C6 inhibit approach of nitrogen to an acyl carbon. In 18 [a bis(silyl)amide], the bulky trimethylsilyl groups sterically block the nitrogen and in this case steric

hindrance and also diminished base strength leads to slow deprotonation for many carbonyl species. Relatively unhindered ketones, aldehydes or esters usually react to form the enolate anion without major problems. The hindered chelating base 1,8-bis(dimethylamino)naphthalene (**19**) is a very poor nucleophile, but extremely efficient at removing protons.¹⁵ It is sold under the name Proton SpongeTM.

It is noted that there are differences in base strength for the amide bases. We can use pK_a for a comparison of the amines, the conjugate acid of the reaction of an amide base and an acid. A stronger base has a conjugate acid with a higher pK_a . If we compare the acetylide anion with hydroxide, the conjugate acid acetylene with a pK_a of about 25 can be compared with water, with a pK_a of 15.7 (see chap. 8, Table 8.16). Since acetylene has the higher pK_a , we can conclude that acetylide is a much stronger base relative to hydroxide. Fraser and Mansour reported that the pK_a of $(Me_3Si)_2NH$ is 29.5, diisopropylamine is 35.7, dicyclohexylamine is 35.7, and 2,2,6,6-tetramethylpiperidine is 37.3, all reported in THF.¹⁶ Therefore, we can compare the base strength of **15**, **17** and **18**. Using the pK_a data, **17** is more basic than **15**, and **18** is the least basic in this series. In water,¹⁷ the pK_a of the conjugated acid of **19** is reported to be 12, but it is 7.47 in DMSO.¹⁸ As a comparison, ammonia has a pK_a of 9.24 (ammonium ion, $NH_3 \rightarrow NH_4^+$),¹⁹ whereas amide (H_2N^-) has a pK_a of 38 (ammonia, $H_2N^- \rightarrow NH_3$),²⁰ both measured in water. Note that this data is consistent with amide being a much stronger base than ammonia.

The structure of LDA is not the monomeric species suggested by structure **15**, but rather an aggregate. Jackman and co-workers,^{21a} and later Seebach and co-workers studied the colligative

- 16. Fraser, R.R.; Mansour, T.S. J. Org. Chem. 1984, 49, 3443.
- 17. Kresge, A.J. Pure. Appl. Chem. 1981, 53, 189.
- 18. Hess, A.S.; Yoder, R.A.; Johnston, J.N. Synlett 2006, 147.
- 19. Bruckenstein, S.; Kolthoff, I.M., in Kolthoff, I.M.; Elving, P.J. Treatise on Analytical Chemistry, Vol. 1, part. 1, Wiley, NY, 1959, pp. 432-433.
- 20. Bunbcel, E.; Menon, B. J. Am. Chem. Soc. 1977, 99, 4457.
- Jackman, L.M.; De Brosse, C.W. J. Am. Chem. Soc. 1983, 105, 4177; (b) Bauer, W.; Seebach, D. Helv. Chim. Acta 1984, 67, 1972; (c) Williard, P.G.; Salvino, J.M. J. Org. Chem. 1993, 58, 1. Also see (d) Shobatake, K.; Nakamato, K. Inorg. Chem. Acta 1970, 4, 485.

^{12.} Olofson, R.A.; Dougherty, C.M. J. Am. Chem. Soc. 1973, 95, 581.

^{13.} Amonoo-Neizer, E.H.; Shaw, R.A.; Skovlin, D.O.; Smith, B.C. J. Chem. Soc. 1965, 2997.

For a discussion of the structure of lithium hexamethyldisilazide, see Lucht, B.L.; Collum, D.B. Acc. Chem. Res. 1999, 32, 1035.

^{15. (}a) Ishida, A.; Mukaiyama, T. Chem. Lett. 1976, 1127; (b) Diem, M.J.; Burow, D.F.; Fry, J.L. J. Org. Chem. 1977, 42, 1801.

properties of LDA as a solution in THF, and concluded that dilute solutions exist as both dimers (20) and monomers (21).^{21b} The structure of LDA in solution is assumed to be the THF solvated dimer shown by



Williard and Salvino's X-ray structure 23,^{21c} that shows the nitrogen may be more sterically encumbered than is suggested in the representation in Figure 9.1. Note that 23 is the same representation as 20 where n = 1. Solution structures of chiral lithium amides having internal sulfide coordination have also been determined, and mixed dimeric complexes are generally formed.²²



Collum and Rutherford studied the solution structure of lithium diethylamide (16) in THF and in ether, where dimers and trimers, and also four-, five- and six-rung ladder structures such as 22 were detected.²³ Collum and Galiano-Roth investigated the aggregation state of LDA in solution during the metalation of *N*,*N*-dimethylhydrazones (sec. 9.4.F.ii) using ⁶Li and ¹⁵N NMR.²⁴ The NMR data also suggested a solvated, dimeric structure such as 20. Collum and DePue found evidence the structure of lithium isopropylcyclohexylamine (LICA) was an equilibrating set of stereoisomeric dimers in solution, cis-24 and trans-24.²⁵ Collum's studies found no evidence for monomeric species in solution, and concluded that 21 was not a significant

species in ether solutions of LDA.^{24,25} Collum and coworker's showed that enolization of ketones with LiN(TMS)₂, in the presence of diisopropyl



^{22.} Sott, R.; Faranander, J.; Dinér, P.; Hilmersson, G. Tetrahedron Asymmetry 2004, 15, 267.

^{23.} Rutherford, J.L.; Collum, D.B. J. Am. Chem. Soc. 1999, 121, 10198.

^{24.} Galiano-Roth, A.S.; Collum, D.B. J. Am. Chem. Soc, 1989, 111, 6772.

^{25.} DePue, J.S.; Collum, D.B. J. Am. Chem. Soc. 1988, 110, 5518, 5524.

ether, substituted tetrahydrofurans, and cineole proceed via dimer-based transition structures.²⁶ The hindered ethers accelerate the enolization by sterically destabilizing the reactants and stabilizing the transition structures. Pratt and co-workers²⁷ found that lithium tetramethylpiperidide (LiTMP) in THF gave the best selectivity for formation of the (*E*)-enolate anion of ketones. Selectivity was improved further by using a LiTMP-butyllithium mixed aggregate. Less polar solvents led to diminished selectivity.

9.2.C. (E/Z) Geometry in Enolate Formation

Formation of an enolate anion from a ketones is often accompanied by formation of (*E*) and (*Z*) isomers. Treatment of 2-methyl-3-pentanone with LDA (THF, -78° C), for example, gave

a 60:40 mixture of the (*Z*) and (*E*) enolates (**25** and **26**)²⁸ Subsequent acyl addition of **25** and **26** to a carbonyl compound (sec. 9.4.A) could lead to different stereochemical consequences, even if the orientation and facial bias of the reaction is



controlled. It is therefore important to understand the factors that control selectivity in enolate forming reactions. Evans' review²⁹ includes a compilation of several studies of selective enolization. Table 9.3.³⁰ shows the influence of structure and base on enolate geometry for simple ketones.

Ν	$Ae \longrightarrow_{O}^{R^1} \frac{\text{LiNR}}{-78}$	₂ , THF → 0°C	$\frac{Me}{(Z)} \stackrel{R^1}{_{O^-L^+_i}} +$	Me (E) 0	R^1
<u>R</u> 1	LiNR ₂ ^a	(Z):(E)	<u>R</u> ¹	LiNR ₂ ^a	(<u>Z) : (E)</u>
Et	LTMP	14:86	<i>i</i> -Pr	LHDS	59:41
Et	LTMP/HMPA	92:8	<i>i</i> -Pr	LTMP	>98:2
Et	LDA	23:77	<i>t</i> -Bu	LDA	32:68
Et	LICA	35 : 65	Ph	LDA	>98:2
Et	LHDS	66 : 34	mesityl	LDA	>98:2
Et	(Me ₂ PhSi) ₂ NLi	100:0	mesityl	LICA	5:95
<i>i</i> -Pr	LDA	60:40	mesityl	LHDS	4:96
<i>i</i> -Pr	LICA	59:41			87:13
 ^a LDA = lithium diisopropylamide (15). LICA = lithium isopropylcyclohexylamide (24). LTMP = lithium 2,2,6,6-tetramethylpiperidide (17). LHDS = lithium hexamethyldisilazide (18) 					

 Table 9.3.
 The Influence of Ketone Structure and Base on Enolate Geometry

26. Zhao, P.; Lucht, B.L.; Kenkre, S.; Collum, D.B. J. Org. Chem. 2004, 69, 242.

- Pratt, L.M.; Newman, A.; St. Cyr, J.; Johnson, H.; Miles, B.; Lattier, A.; Austin, E.; Henderson, S.; Hershey, B.; Lin, M.; Balamraju, Y.; Sammonds, L.; Cheramie, J.; Karnes, J.; Hymel, E.; Woodford, B.; Carter, C. J. Org. Chem. 2003, 68, 6387.
- 28. Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.A.; Sohn, J.E.; Lampe, J.J. Org. Chem. 1980, 45, 1066.
- 29. Evans, D.A. in *Asymmetric Syntheses, Vol. 3*, Morrison, J.D. Ed., Academic Press, New York, *1984*, pp 1-110. 30. Reference 29, p 16.

Only moderate variations in kinetic (E/Z) ratios are observed, except when LHDS was used as the base, which favored the thermodynamically more stable (Z) enolate. The sterically demanding base LTMP favored formation of the kinetic E enolate.³¹ This equilibration may involve an aldol addition–retro-aldol process as suggested by Rathke and co-workers (via **27**).³¹ The **aldol condensation** is discussed in Section 9.4.A. Addition of HMPT (hexamethylphosphorus triamide) destabilizes and deaggregates aldolate **27**, thus promoting equilibration.



The (E/Z) trends observed for ketones is also seen in enolate anions of esters and amides, as shown in Table 9.4.³² The kinetic (E) ester enolate usually predominates with esters unless HMPT is added,³³ but amides³⁴ give the thermodynamic (Z) isomer. It is unlikely that the equilibration observed with ketones is responsible for reversal in enolate geometry in esters on addition of HMPT. Such equilibration would show a preference for formation the (Z)enolate with both LDA and sec-butyllithium, and would lead to significant amounts of Claisen condensation (sec. 9.4.B.i). The influence of the dialkylamide base and the carbonyl structure on the (E/Z) enolate ratio can be rationalized by the so-called **Ireland model**.^{33,35} where the two important steric factors are taken to be R¹ versus Me in 29 and Me versus L in 31 (see Table $(9.5)^{36}$ and the Zimmerman-Traxler model in sec. (9.5, A.iii). This model was developed to predict stereochemistry in the anionic accelerated Claisen rearrangement (sec. 11.12.D.ii), but is used for predicting stereochemistry in ester enolates. Enolate anions actually exist as aggregate dimers, tetramers or hexamers (sec. 9.2.D), so this model has some limitations. It generally gives good predictions, and is also a useful tool for predicting (E) and (Z) isomers for enolate anions. When R^1 is not sterically demanding (as in OR) the H \leftrightarrow L interaction in 28 is much smaller than the Me \leftrightarrow L interaction in **30** and more of the (E) isomer (**29**) is produced. When R^1 is large (such as *tert*-butyl) the large Me $\leftrightarrow R^1$ interaction in **28** is larger than the H $\leftrightarrow R^1$ interaction and usually larger than the Me \leftrightarrow L interaction in 30. In this case, 30 is favored, leading to an increased amount of the (Z) isomer (31). It is possible that addition of HMPT disrupts the pericyclic transition states represented by 28 and 30.

 ⁽a) Fataftah, A.Z.; Kopka, I.E.; Rathke, M.W. J. Am. Chem. Soc. 1980, 102, 3959; (b) also see Nakamura, E.; Hashimoto, K.; Kuwajima, I. Tetrahedron Lett. 1978, 2079.

^{32.} Reference 29, p 17 and references 39, 40, 45-47 therein.

^{33.} Ireland, R.E.; Mueller, R.H.; Willard, A.K. J. Am. Chem. Soc. 1976, 98, 2868.

^{34.} Reference 29, p 17.

^{35.} Reference 29, pp 18-20.

 ⁽a) Reference 29, p 19; also see (b) Meyers, A.I.; Snyder, E.S.; Akerman, J.J.H. J. Am. Chem. Soc. 1978, 100, 8136; (c) Hoobler, M.A.; Bergbreiter, D.E.; Newcomb, M. Ibid. 1978, 100, 8182; (d) Davenport, K.G.; Eichenauer, H.; Enders, D.; Newcomb, M.; Bergbreiter, D.E. Ibid. 1979, 101, 5654.

	R ²	$\operatorname{M}^{\mathrm{R}^1}_{\mathrm{O}}$ LiN_{-78}	$\xrightarrow{R_2, THF} \rightarrow 0^{\circ}C$	$R^2 \xrightarrow{(Z)}_{O^- Li^+} R^1 +$	R ²	$(E) \stackrel{R^1}{\searrow} ^{R^1} $	
<u>R</u> 1	<u>R</u> ²	LiNR ₂	(<u>Z) : (E)</u>	<u>R</u> ¹	<u>R</u> ²	LiNR ₂	(<u>Z) : (E)</u>
OMe	Me	LDA	5:95	Ot-Bu	Et	LDA, HMPT	77:23
OCH ₂ OMe	Me	LDA	<2:98	St-Bu	Me	LDA	10:90
Ot-Bu	Me	LDA	5:95	NEt ₂	Me	LDA	>97:3
OMe	Et	LDA	9:91	NEt ₂	Me	sec-BuLi	75:25
OMe	Et	LDA, HMPT	84:16	Pyrrolidino	Me	LDA	>97:3
Ot-Bu	Et	LDA	5 : 95	Pyrrolidino	Me	sec-BuLi	80:20

Table 9.4. Enolate Geometry of Esters and Amides

 Table 9.5.
 Formation of (E) and (Z) Enolates and the Ireland Model



9.2.D. Structure and Aggregation State of Enolate Anions

Enolate geometry must is a function of the structure of the enolate anion. Metal enolates exist as dimers^{37a} or other aggregates in ether solvents³² (see Section 9.2.C. for LDA aggregates).^{37d} Jackman and Szeverenyi suggested that the lithium enolate of isobutyrophenone exists as a tetramer (**32**) in THF solution,³⁸ but as a dimer (**33**) in DME.³⁹ House et al proposed these aggregates,⁴⁰ and found that ketone enolates of groups 1, 2 and 3 metals exist primarily as the *O*-metal enolate.^{41,39} For lithium enolates, increasing the donor properties of the solvents

 ⁽a) Bernstein, M.P.; Collum, D.B. J. Am. Chem. Soc. 1993, 115, 789; (b) Bernstein, M.P.; Romesberg, F.E.; Fuller, D.J.; Harrison, A.T.; Collum, D.B.; Liu, Q.Y.; Williard, P.G. Ibid. 1992, 114, 5100; (c) Collum, D.B.Acc. Chem. Res. 1992, 25, 448; (d) Reference 29, p 21 and citations 59-64 therein.

 ⁽a) Jackman, L.M.; Szeverenyi, N.M. J. Am. Chem. Soc. 1977, 99, 4954; (b) Jackman, L.M.; Lange, B.C. Ibid. 1981, 103, 4494.

^{39.} Jackman, L.M.; Lange, B.C. Tetrahedron 1977, 33, 2737.

^{40.} House, H.O.; Gall, M.; Olmstead, H.D. J. Org. Chem. 1971, 36, 2361.

 ⁽a) House, H.O.; Auerbach, R.A.; Gall, M.; Peet, N.P. J. Org. Chem. 1973, 38, 514; (b) Orsini, F.; Pelizzoni, F.; Ricca, G. Tetrahedron Lett. 1982, 23, 3945; (c) House, H.O.; Prabhu, A.V.; Phillips, W.V. J. Org. Chem. 1976, 41, 1209.

from ether \rightarrow THF \rightarrow DME increases the Li–O bond polarization, enhancing the α -carbon π -electron density.⁴² An increase in π -electron density is also observed for the series: Li \rightarrow Na \rightarrow K. Increasing π -electron density is associated with greater reactivity of carbon in the enolate alkylation reactions.⁴³



Lithium enolate anions of ketones exist as aggregates in solution.^{38-40,43d,44} Mixed aggregates between the enolate anion and the amide base are also possible.⁴⁵ In 1981, Seebach and co-workers confirmed by X-ray crystallography that the lithium enolates of pinacolone and cyclopentanone form a tetrameric aggregate in the solid state, and it was assumed that a similar species exited in solution.⁴⁶ A THF solvated tetramer of lithium pinacolonate is shown (see **34**), as reported by Seebach.⁴¹ Williard et al. reported the X-ray structure of the unsolvated lithium enolate of pinacolone to be a hexamer (**35**).⁴⁷ The structure of the potassium enolate of pinacolone was a hexamer, although the sodium enolate was a tetramer. The tetramer was composed of a cubic cluster of four enolized ketone molecules, four sodium atoms, and four *unenolized* solvating ketones units, which contrasts with **35** in which each oxygen atom is coordinated to three lithium atoms, and each enolate double bond is almost antiperiplanar to one lithium atom. A variety of X-ray crystal structures for organolithium derivatives confirm the presence of aggregates in the solid state.⁴⁸ There is also evidence that the aggregate structure is preserved in solution and is probably the actual reactive species.^{2b}

- 44. Stork, G.; Hudrlik, P.F. J. Am. Chem. Soc. 1968, 90, 4464.
- 45. Sun, C.; Williard, P.G. J. Am. Chem. Soc. 2000, 122, 7829.
- 46. (a) Amstutz, R.; Schweizer, W.B.; Seebach, D.; Dunitz, J.D. *Helv. Chim. Acta* **1981**, *64*, 2617; (b) Seebach, D.; Amstutz, D.; Dunitz, J.D. *Ibid.* **1981**, *64*, 2622.
- 47. (a) Williard, P.G.; Carpenter, G.B. J. Am. Chem. Soc. 1986, 108, 462; (b) Williard, P.G.; Carpenter, G.B. Ibid. 1985, 107, 3345.

^{42.} Reference 29, p 22.

 ⁽a) Zook, H.D.; Gumby, W.L. J. Am. Chem. Soc. 1960, 82, 1386; (b) Zook, H.D.; Russo, T.J. Ibid. 1960, 82, 1258; (c) Zook, H.D.; Russo, T.J.; Ferrand, E.F.; Stotz, D.S. J. Org. Chem. 1968, 33, 2222; (d) Zook, H.D.; Kelly, W.L.; Posey, I.Y. Ibid. 1968, 33, 3477; (e) Zook, H.D.; Miller, J.A. Ibid. 1971, 36, 1112.

For example, see (a) Bauer, W.; Laube, T.; Seebach, D. Chem. Ber. 1985, 118, 764; (b) van Koten, G.; Jastrzebski, J.T.B.H. J. Am. Chem. Soc. 1988, 107, 697; (c) Polt, R.L.; Stork, G.; Carpenter, G.B.; Williard, P.G. Ibid. 1984, 106, 4276; (d) Amstutz, R.; Laube, T.; Schweizer, W.B.; Seebach, D.; Dunitz, J.D. Helv. Chim. Acta 1984, 67, 224.





Seebach et al. showed that lithium enolates derived from esters are aggregates. The lithium enolates of (*Z*)-*tert*-butyl propionate (**36**) and of *tert*-butyl-2-methylpropionate are dimers in the solid state.⁴⁹ In both cases, the crystal contains two coordinated TMEDA molecules (see **36**). The lithium enolate of (*Z*)-methyl 3,3-dimethylbutanoate was found to be a dimer containing four THF molecules. Focusing on colligative properties rather than X-ray analysis, Collum and co-workers determined that lithium 2-carbomethoxycyclohexanone dimethylhydrazone (sec. 9.4.F.ii) is a dimeric THF solvate in the solid state.⁵⁰ *Perhaps the most important implication of this work is that the reactivity of enolate anions in alkylation and condensation reactions (see below) will be influenced by the aggregate state of the enolate. If the enolate anion is are attached to (or a part of) a tetrameric or hexameric complex, then simple steric*

^{49.} Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W.B.; Dunitz, J.D. J. Am. Chem. Soc. 1985, 107, 5403.

 ⁽a) Wanat, R.A.; Collum, D.B.; Van Duyne, G.; Clardy, J.; De Pue, R.T. J. Am. Chem. Soc. 1986, 108, 3415;
 (b) Wanat, R.A.; Collum, D.B. Ibid. 1985, 107, 2078.

and electronic arguments for reactivity and selectivity are flawed if they are based only on examining monomeric species. The relative proportions of (E) and (Z) enolate anions will be influenced by the extent of solvation and the aggregation state.

The solvent plays a significant role in the aggregation state of enolate anions, and this directly influences their reactivity. Streitwieser et al. found that selected lithium enolate anions have lower aggregation states in dimethoxyethane than in THF, and that aggregation is much higher in methyl *tert*-butyl ether.⁵¹ He found that alkylation and acylation of the enolate anions was extremely slow in methyl *tert*-butyl ether. These reactions apparently require additional solvation of the lithium cation, which is ineffective in this solvent.

Once formed, an enolate anion can react with a variety of electrophiles. The approach of the electrophile is usually assumed to be perpendicular (as in **37**), in reactions with alkyl halides and epoxides, to maximize overlap of participating orbitals.⁵² This model also applies to the deprotonation reaction. The LUMO of the electrophile is important, and Dunitz and co-workers⁵³ showed that a non-vertical approach (represented by **38** or **39**)⁵⁴ is preferred when nucleophiles attack carbonyl centers. The angle of approach (as discussed in secs. 4.7.C, sec. 6.6.A. and 9.2.B) is ~ 110° and is called the **Bürgi-Dunitz trajectory**.^{11,53} Models **38** and **39** imply that as

the enolate nucleophile approaches the carbonyl carbon, the approach angle is somewhat restricted, which enhances the steric effects between R and the approaching electrophile. Since the geometry of the enolate



will influence the approach of the electrophile, geometric constrictions must be considered when examining stereoselectivity. It appears that enolate-alkyl halide transition states are essentially reactant-like, and that the product stereochemistry is determined largely by steric factors.



^{51.} Streitwieser, A.; Juaristi, E.; Kim, Y.-J.; Pugh, J.K. Org. Lett. 2000, 2, 3739.

^{52. (}a) Reference 29, p 25; (b) Velluz, L.; Valls, J.; Nominé, G. Angew. Chem. Int. Ed. 1965, 4, 181 (see p 189);
(c) Valls, J.; Toromanoff, E. Bull Soc. Chim. Fr. 1961, 758; (d) Toromanoff, E. Ibid. 1962, 708, 1190; (e) Bucourt, R. Ibid. 1964, 2080; (f) Toromanoff, E.; Bucourt, R. Tetrahedron Lett. 1976, 3523.

 ⁽a) Bürgi, H.B.; Dunitz, J.D.; Lehn, J.M.; Wipff, G. *Tetrahedron* 1974, 30, 1563; (b) Bürgi, H.B.; Dunitz, J.D.; Shefter, E. J. Am. Chem. Soc. 1973, 95, 5065; (c) Bürgi, H.B.; Lehn, J.M.; Wipff, G. *Ibid.* 1974, 96, 1956; (d) Bürgi, H.B. Angew. Chem. Int. Ed. 1975, 14, 460.

^{54. (}a) Agami, C. *Tetrahedron Lett.* **19**77, 2801; (b) Agami, C.; Chauvin, M.; Levisalles, J. *Ibid.* **1979**, 1855; (c) Agami, C.; Levisalles, J.; Lo Cicero, B. *Tetrahedron* **1979**, *35*, 961.

Lithium enolate anions exist as large aggregates, and their approach to the electrophile is restricted by steric and electronic considerations, as well as by the relative geometry of the molecule. Nonetheless, good predictions for reactivity and diastereoselectivity can be made based on the steric requirements that would be present in a monomeric system. For example, in most reactions of enolate anions the electrophile will be delivered to the less hindered face of the enolate to give the major product. In all models used to describe reactivity (secs. 9.5.A.iii-9.5.A.v), a monomeric enolate will be shown but the facial and orientational bias of the enolate is clearly influenced by the state of aggregation in solution.

9.2.E. Kinetic Versus Thermodynamic Control

In an unsymmetrical ketone, the protons on both sides of the carbonyl are acidic (H_a and H_b in 1), and the p K_a values of the protons are different. When such a ketone is treated with an appropriate base, removal of the different protons will lead to different regioisomeric enolates.

3-Hexanone (40), for example, reacted with LDA to give a mixture of 41 and 42, and each enolate anion is a mixture of *E* and *Z* isomers. In 40, each α -carbon has one alkyl substituent (methyl and ethyl, respectively). In many cases, however, the



α- and α'-carbon can be monosubstituted or disubstituted. The α-protons at each carbon will have slightly different pK_a values, with the less substituted position having the more acidic proton. As noted in Table 9.1, 3,3-dimethyl-2-butanone (**4**, O=C–C<u>H</u>₃) has a pK_a of 20.8 and 4,4-dimethyl-3-pentanone (**5**, O=CC<u>H</u>₂CH₃) has a pK_a of 21.7. In general, the difference in pK_a for monosubstituted versus disubstituted positions is typically only about 1 pK_a unit. 2-Methyl-3-pentanone (**43**) has two acidic protons, H_a and H_b. As discussed previously, the methyl group releases electrons to the carbon bearing H_b, reducing the acidity of H_b by about 1 pK_a unit relative to H_a. Removal of H_a leads to enolate **44**, and loss of H_b leads to enolate **45**. Enolate



44 results from loss of the most acidic proton, which is removed faster in an acid-base reaction to give the **kinetic** enolate anion (less stable). Enolate 45 is the more thermodynamically stable, but it

is formed only after equilibration of the initially formed enolate anion and is known as the **thermodynamic** enolate anion. This observation raises the question if it is possible to form one enolate or the other regioselectively. It is noted that 44 can be formed as a mixture of (E) and (Z) isomers. The (E/Z) ratio is one of the parameters that can be controlled to influence selectivity in diastereoselective aldol condensation reactions, discussed in section 9.5.

MOLECULAR MODELING: Acidity of Hydrogens Attached to a Carbons in Ketones

It is well known that the pK_a of the proton on the α -carbon of a ketone is influenced by substituents on that carbon. Alkyl substituents are electron releasing and halogens, alkoxy groups, amino groups and carbonyl groups are electron withdrawing.

Two different types of proton are identified for each of compounds A-D shown below.



Construct **A**, and obtain an electrostatic potential map. This displays the energy that a positive charge feels at a location on the surface of a molecule. Areas for which the charge is repelled are colored blue and are associated with more electrophilic atoms. Compare the surface around H_a and H_b . Which hydrogen appears to be the more acidic (more blue)? *Click* on > to the right of the tab at the top of the screen and select **Continue** to bring up a fresh builder palette without removing this text. Build **B**, obtain its electrostatic potential map and determine the relative acidities of H_a and H_b . Which is more acidic? What is the influence of the methyl group in **B** when compared with **A**? Repeat the sequence (*click* on > and select **Continue**) to build **C** and obtain its electrostatic potential map. Which of the two hydrogens, H_a or H_b , is more acidic? What does this tell you about the influence of the chlorine? Repeat one last time to make **D**, obtain its electrostatic potential map and determine the relative acidities of the second carbonyl group on acidity?

Display all four compounds simultaneously on screen. *Check* the box to the left of each of the four tabs at the top of the screen. Which of the four compounds shown is likely to have the most acidic proton? Elaborate.

Enolate formation is an acid-base reaction (sec. 2.2.A), and control of this equilibrium is the key to regioselectivity. As with any acid-base reaction, the equilibrium is determined by the relative strengths of the acid-base and conjugate acid-conjugate base pairs. Reaction of a strong acid and a strong base generates a weak conjugate acid-weak conjugate base, and K_a is large. If the conjugate acid and conjugate base are stronger than the initial acid-base pair, K_a is small. A typical acid-base equilibrium reaction is shown for the reaction of **46** to give **47**.

$$\begin{array}{cccc} O & Acid & Base \\ R & \downarrow & R \\ \hline \mathbf{46} & H \end{array} \xrightarrow{R} + B: \\ \hline \mathbf{46} & H \end{array} \xrightarrow{K_1} \\ \hline \mathbf{46} & \mathbf{K}_1 \\ \hline \mathbf{47} \\ \hline \mathbf{47} \\ \hline \mathbf{10} \\ \mathbf{47} \\ \hline \mathbf{10} \\ \mathbf{47} \\ \hline \mathbf{10} \\ \mathbf{10} \\$$

Kinetic control means that the kinetic enolate is the major product (K_a is large and $k_1 >> k_{-1}$). Thermodynamic or equilibrium control means the thermodynamic enolate is the major product, and K_a is near unity. The choice of solvent, base, cation and temperature equilibrium control K_a . *Kinetic control* is favored by several factors,² including (1) aprotic solvents, (2) strong bases that are weakly nucleophilic and generate a conjugate acid that is weaker than the ketone or aldehyde, (3) cations such as Li which complex oxygen: (not Na⁺ or K⁺), (4) low temperatures, and (5) short reaction times. The conditions that favor thermodynamic control must be the opposite of those described for kinetic control.² *Thermodynamic control* conditions include (1) protic solvents, (2) nucleophilic bases that generate a conjugate acid that is stronger than the ketone or aldehyde, (3) cations that form ionic M–O bonds, (4) higher temperatures, and (5) long reaction times. These parameters can be explained by examining the three species involved in the equilibrium, 43-45. For kinetic control (formation of 44), the reaction should be essentially irreversible and the reaction conditions should suppress the equilibrium.



Solvents can be grouped according to whether or not they have an acidic proton. Protic solvents (solvents containing an acidic hydrogen), usually involve O–H, S–H or N–H and promote equilibrium conditions (small pK_a). Remember than a $K_a = 1$ represents a 50:50 equilibrium. Aprotic solvents favor a large K_a (an equilibrium that is shifted to the right). In the reaction of **46**, the ketone is the acid (p $K_a \sim 21$) and a protic solvent such as ethanol (p $K_a \sim 17$) or water (p $K_a \sim 15.8$) will be a stronger acid. Once the conjugate base (the enolate anion, **47**) is formed, it reacts with the protic solvent to regenerate the ketone, driving the equilibrium to the left (small K_a). Aprotic solvents such as THF do not have an acidic proton and the enolate anion cannot react with them, meaning that once formed the enolate anion will be relatively stable (equilibrium shifted to the right, large K_a). In other words, aprotic solvents such as ether or THF favor kinetic control, and protic solvents such as ethanol, water, methanol or *tert*-butanol favor thermodynamic control.

MOLECULAR MODELING: Solvent Effects on Enolate Formation

In solution, the reaction of 2-methylcyclopentanone with a base leads to the enolate anion that results from deprotonation at the less substituted C_5 position, and not the more substituted C_2 position. In other words, the protons on C_5 are more acidic than the proton on C_2 . This observation suggests that the proton on the carbon bearing the methyl group, the more substituted C_5 carbon, is less acidic. The usual explanation for this observation is that the methyl group is an electron donor, and it acts to destabilize the anionic center to which it is attached. However, the fact that a methyl group is larger than hydrogen suggests that it might also act to disperse the negative charge and actually lead to stabilization of the carbanion center.

MOLECULAR MODELING: Solvent Effects on Enolate Formation, con't.

Such interpretations can be tested by quantum chemical calculations. Given that the calculations strictly correspond to measurements carried out in the gas phase, do they necessarily lead to the same results as measurements carried out in solution? In other words, they may not conclude that the methyl group actually has a destabilizing effect on the carbon to which it attached. To explore this, compare energies for the two possible enolate anions resulting from deprotonation of 2-methylcyclopentanone. First build the enolate anion corresponding to deprotonation at the less substituted carbon (C₂). You can easily do this by using icons for sp², sp³ and anionic carbons and sp² oxygen. Obtain its energy using the properties icon. Now make the enolate anion for deprotonation at C₅ (the more substituted carbon), and obtain the energy. *Click* on > at the right of the tab at the top of the screen and select *Continue* to bring up a fresh builder palette while maintaining this text. Compare energies of the two. Which enolate anion is more stable? Is this result consistent with destabilization of the anionic center by the methyl group? If it is not, provide a plausible interpretation of the experimental result.

Whether or not the methyl group is actually an electron donor pushing more negative charge onto the carbanion center or just a "bulky" group dispersing the negative charge, it's overall effect on a carbanion center would be expected to be modest. Change it for a methoxy group (presumably a much stronger electron donor). Start each by *clicking* on > to the right of the tab at the top of the screen and selecting **Continue**. Which enolate anion is favored here and by how much? Is there a significant change from what you observed for methyl?

Finally, repeat your calculations and analysis for the two enolate anions formed by deprotonation of 2-phenylcyclopentanone. Start each by *clicking* on > to the right of the tab at the top of the screen and selecting **Continue**. Which enolate anion is favored? What does your result say about the effect of a phenyl group on a carbanion center? Is the magnitude of the preference smaller, larger or about the same as that for 2-methylcyclopentanone? Rationalize your result.

The base plays two roles in this reaction. First, it must react with the acid (see **43**) quickly and efficiently (it must be a strong base). The base also generates a conjugate acid after deprotonation that plays a significant role in the position of the overall equilibrium. If the conjugate acid is more acidic than **43**, it will reprotonate the conjugate base (the enolate anion) and drive the equilibrium back toward **43**. When LDA deprotonates **43** to form **44** *in an aprotic solvent*, the only acids in the equilibrium are **43** ($pK_a \sim 21$) and diisopropylamine ($pK_a \sim 25$), the conjugate acid formed by reaction with LDA. Since diisopropylamine is a weaker acid than the ketone, reaction with the enolate anion (the conjugate base) is relatively slow, which shifts the overall equilibrium to the right (large K_a) and favors kinetic enolate formation. Note that diisopropylamine is a weak acid, and given sufficient time it will react with the enolate anion to establish an equilibrium (see below). If the reaction is done in THF with sodium ethoxide as the base, enolate **44** is also formed since H_a is the most acidic proton. The pK_a of this ketone acid is ~ 21 (as mentioned, see Table 9.1), but as ethoxide reacts with **43** it generates ethanol as the conjugate acid with a $pK_a \sim 17$. Ethanol easily reacts with the enolate anion, shifting the equilibrium to the left so that **43**, ethoxide, ethanol and some **44** are all in solution. Although H_b in 43 is less acidic than H_a , it is acidic enough to be removed by ethoxide. If the conversion of 43 to 44 is slow and/or reversible, the less acidic H_b will be removed to generate enolate anion 45. The conjugate acid (ethanol) will reprotonate 45, establishing a second equilibrium between 44 and 45. If the solvent is ethanol, which is a stronger acid than 43, this equilibrium is favored and as mentioned, 43-45, ethanol and NaOEt will all be in solution. The C=C unit of enolate anion 45 is more highly substituted and assumed to be thermodynamically more stable. Therefore, once is established, the equilibrium will shift to favor the more stable enolate anion 45 (hence the term thermodynamic control). This discussion can be summarized by saying that strong bases such as LiNH₂ or LiNR₂ favor kinetic control, since they generate weak conjugate acids, but strong bases such as NaOH, NaOMe, NaOEt or NaO*t*-Bu will favor thermodynamic control because they generate conjugate acids that are stronger than the starting ketone.



The counterion (M⁺) of the base (M⁺NR₂⁻) will be the counterion of the enolate anion unless another metal ion is added. The covalent character of the M–O bond in the enolate plays a role in the kinetic versus thermodynamic equilibrium. If the M–O bond is relatively covalent (as with the Li–O bond), the initially formed enolate (44) will form more easily and be less likely to react with an acid to give 43, which favors the kinetic process. If the M–O bond is more ionic (M = Na, K), the ionic character of the enolate increases and it becomes increasingly easier to reprotonate the anionic oxygen to give 44. This promotes the equilibrium. This relationship is summarized and reinforced by noting that sodium and potassium enolates equilibrate readily, whereas magnesium, lithium, zinc, copper or aluminum enolates favor kinetic control.⁵⁵

Reaction temperature is another important variable. If the reaction is kept cold, all reactions (including the forward and reverse reactions that constitute the equilibrium) are slowed. If there is enough energy at low temperatures to convert **43** to **44**, the subsequent acid-base reactions (that will promote the equilibrium) will be slower, which favors kinetic control. Typical reaction temperatures are -78° C (CO₂ in acetone or 2-propanol) and -100° C (ether in CO₂).⁵⁶ Conversely, high reaction temperatures promote the equilibrium process. In most cases, the temperatures observed with thermodynamically controlled reactions are the reflux temperatures of the solvent (refluxing ethanol, water, methanol, *tert*-butanol).

The final parameter in this process is the length of time the molecules are allowed to react. If the reaction time is short (typically min to h), it is more difficult for the equilibration process to develop. If the reaction is allowed to go for a long time (typically hours to days, although

^{55. (}a) Stork, G.; Rosen, P.; Goldman, N.; Coombs, R.V.; Tsuji, J. J. Am. Chem. Soc. 1965, 87, 275; (b) Patterson, Jr., J.W.; Fried, J.H. J. Org. Chem. 1974, 39, 2506.

^{56.} Gordon, A.J.; Ford, R.A. The Chemist's Companion, John Wiley & Sons, London, 1972. p 451.
minutes can be a long time in some reactions), equilibration and thermodynamic control is more likely. The time factor is linked to the relative strength of all acids in the system. When **44** is formed by reaction of LDA and **43**, its conjugate acid is diisopropylamine. Diisopropylamine is a weak acid, and when given a sufficiently long contact time with a strong base (the enolate anion is a strong base) some acid-base equilibration can occur. Few reactions are quantitative, and virtually none are instantaneous. Remember that about six half-lives are required for a reaction to be >98% complete. Therefore, unreacted starting material will be available during the course of the reaction. Further, if the conversion of **43** to **44** occurs in only 90%, then 10% of unreacted ketone remains. With a pK_a of ~ 21, **43** is acidic enough to reprotonate **44** and establish the equilibrium required for thermodynamic control, if given sufficient time. If the reaction itself is slow, enolate **44** is being formed in the presence of unreacted **43** and there is the possibility of a reaction. The terms short and long are obviously relative and vague, and vary with the electrophile for a particular enolate anion. In general, short reaction times favor kinetic control and long reaction times favor thermodynamic control.

The intramolecular cyclization reaction of bromoketone 48^{57} illustrates how changing reaction conditions can influence formation of the kinetic or thermodynamic enolate. The reaction of 48 with LDA (ether, 0°C) generates the kinetic enolate (49). Subsequent intramolecular displacement of the bromide by the enolate anion gives cyclohexanone 50. Some elimination of 49 under the reaction conditions occurred, giving 52. A complicating factor in this example is that the oxygen in 49 is also a nucleophile, and *O*-alkylation (discussed in sec. 9.3.B) gave the pyran product 51, although 50 was the major product. When 48 was treated with *tert*butoxide in *tert*-butanol, the thermodynamic enolate (53) was formed and this cyclized to the dihydropyran 51 via *O*-alkylation. A four-membered ring product (54) would be the normal enolate alkylation product that is analogous to 50, but its formation has a relatively high activation barrier and it was a minor product (secs. 1.5.B, 6.6.B).



^{57. (}a) House, H.O.; Philips, W.V.; Sayer, T.S.B.; Yau, C.-C. J. Org. Chem. 1978, 43, 700; (b) Etheredge, S.J. Ibid. 1966, 31, 1990.

Carbonyl compounds other than ketones readily form enolate anions. It was noted in Table 9.1 that the α -hydrogen of an aldehyde was more acidic than that of a ketone. When aldehydes are used, however, there is only one acidic proton, and in principle, either kinetic or thermodynamic control conditions can be used. Formation of (*E*) or (*Z*) isomers of **55** remains a problem, however. It may be desirable to use kinetic



control conditions to control geometry, or minimize subsequent reactions such as nucleophilic addition of the conjugate base to the carbonyl (an aldol-type condensation), which is more facile with aldehydes than with ketones (sec. 9.4.A). A nonnucleophilic base such as LTMP often maximizes formation of the enolate. Acid derivatives such as esters and *N*,*N*-disubstituted amides have only one acidic α -proton, and deprotonation gives a single regioisomeric enolate. Methyl butanoate reacted with LDA, for example, to give enolate **56** as a mixture of (*E*) and (*Z*) isomers. Self-condensation is a problem with esters (see section 9.4.B.i).

When primary or secondary amides are treated with a base, there is a complicating reaction that was not possible with esters, ketones or aldehydes. The N–H moiety is acidic enough to react with the bases used for deprotonation. Treatment of **57** with base gave the *N*-lithio derivative, but the α -lithio derivative (**58**) can be generated by addition of two equivalents of base.⁵⁸ Enolate anion formation is straightforward with tertiary amides such as dimethylisobutyramide (**57**, R = Me), and the resultant enolate anion (**59**) reacted with butanal to give amido-alcohol **60** in 68% yield⁵³ (see sec. 9.4.B).



When an ester has an acetyl at the β -position (keto-ester **61**), it is possible to form a dianion. Subsequent reactions will occur first at the site of the second deprotonation, which is more nucleophilic. In the synthesis of stemonamide by Kende and co-workers,⁵⁹ methyl acetoacetate was treated with NaH and then with butyllithium to give dianion **61**. The sodium hydride deprotonated the most acidic hydrogen between the two carbonyl groups, and butyllithium removed the less acidic proton adjacent to the methyl group. This latter carbon is more nucleophilic, and reaction with allyl bromide followed by quenching with an aqueous workup

 ⁽a) Cuvigny, T.; Hullot, P.; Larchevêque, M.; Normant, H. C.R. Hebd. Seances Acad. Sci., Ser. C 1974, 279, 569; (b) Hullot, P.; Cuvigny, T.; Larchevêque, M.; Normant, H. Can. J. Chem. 1976, 54, 1098; (c) Crouse, D.N.; Seebach, D. Chem. Ber. 1968, 101, 3113.

^{59.} Kende, A.S.; Hernando, J.I.M.; Milbank, J.B.J. Tetrahedron 2002, 58, 61.

led to 62 in >90% yield.

All ketones, aldehydes, and esters mentioned so far have had an α -carbon with a hydrogen that could be removed by base. When a ketone does not have such a proton (it is a non-enolizable ketone), treatment with strong base can lead to a C–C bond cleavage reaction. Discovered by Semmeler,⁶⁰ Haller and Bauer⁶¹ developed the reaction illustrated by reaction of **63** with NaNH₂ to give amide **65**. Acyl addition of the amide anion to the carbonyl of the ketone led to **64**, and loss of the anion Ph⁻ gave the amide product. Treatment with aqueous acid (the workup) will protonate the anion to give benzene. This reaction is known as the **Haller-Bauer reaction**.⁶²



9.3. REACTIONS OF ENOLATE ANIONS WITH ELECTROPHILES

There are two major reactions of enolates: (1) displacement reactions with alkyl halides or other suitable electrophiles and (2) nucleophilic acyl addition to carbonyl compounds. Reaction of enolate anion **61** with allyl bromide to give **62**, and reaction of **59** with butanal to give **60** are simple examples. Enolate anions are carbon nucleophiles, and react similarly to the acetylides discussed in section 8.3.C. The reactions discussed in this section are solution-phase enolate anion reactions. Solid-phase enolate anion reactions⁶³ have been investigated⁶⁴ by high resolution-magic angle spinning NMR spectroscopy.

9.3.A. Enolate Alkylation

An enolate anion is a nucleophile, and both the oxygen and the carbon are nucleophilic (sec. 9.3.B), but the reaction at carbon usually predominates. Unlike Grignard reagents and

^{60.} Semmler, F.W. Berichte 1906, 39, 2577.

^{61.} Haller, A.; Bauer, E. Compt. Rend. 1908, 147, 824.

^{62. (}a) Hamlin, K.E.; Weston, A.W. Org. React 1957, 9, 1; (b) Mehta, G.; Venkateswaran, R.V. Tetrahedron 2000, 56, 1399; (c) Paquette, L.A.; Gilday, J.P. Org. Prep. Proceed. Int. 1990, 22, 167.

^{63.} See Dörwald, F.Z. Organic Synthesis on Solid Phase, Supports, Linkers, Reactions, Wiley-VCH, New York, 2000, Chapters 12-13.

^{64.} Fruchart, J.-S.; Lippens, G.; Kuhn, C.; Gras-Masse, H.; Melnyk, O. J. Org. Chem. 2002, 67, 526.

organolithium reagents enolate anions react easily with the electrophilic carbon of an alkyl halide.⁶⁵ As with acetylides (sec. 8.3), reaction an alkyl halide with an enolate anion forms a new carbon-carbon bond with concomitant formation of a metal halide (M–X).

Many synthetic applications involve enolate alkylation. In Funk and Greshocks synthesis of welwistatin,⁶⁶ cyclohexanone **66** was treated with lithium hexamethyldisilazide to generate the enolate anion, and addition of allylic bromide **67** gave the alkylated ketone **68** in 75% yield, with >10:1 selectivity for the diastereomer shown. Note that HMPA [hexamethylphosphoramide, (Me₃N)₃P=O] was added to facilitate formation of the anion and also to assist the alkylation step. Another example is the reaction of **69** with LDA to give enolate **70**, where the lithium is chelated with the nitrogen lone pair electron.⁶⁷ The facial bias imposed by the stereogenic centers, and the relatively rigid conformation of **70** led to reaction from the bottom face (the α face in steroid nomenclature). Addition of 1-bromo-2-cyclohexene from this less sterically hindered face led to **71** with high diastereoselectivity (>95:<5 favoring the stereochemistry shown for **71**).⁶⁷



In some alkylation reactions, HMPA (hexamethylphosphoramide) is used as an additive to facilitate the alkylation. Hexamethylphosphorus triamide [HMPT, $(Me_2N)_3P$] also coordinates with the enolate anion, thereby diminishing the aggregate state and increasing reactivity. This additive also enhances solvent polarity and enhances the facility of an S_N2 alkylation step (sec. 2.6.A.i). The use of additives such as HMPA or HMPT is very common when the enolate anion reacts slowly, and/or the halide is relatively unreactive. Other acid derivatives such as lactones can react with LDA to give an enolate anion, which then reacts with alkyl halides in the usual manner.

^{65.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd ed., Wiley-VCH, New York, 1999, pp 1476-1483.

^{66.} Greshock, T.J.; Funk, R.L. Org. Lett. 2006, 8, 2643.

^{67.} Thottathil, J.K.; Moniot, J.L.; Mueller, R.H.; Wong, M.K.Y.; Kissick, T.P. J. Org. Chem. 1986, 51, 3140.

The general disconnections for enolate alkylation are

$$R \xrightarrow{O}_{R^{1}} R \xrightarrow{O}_{R} \xrightarrow{O}_{R} \xrightarrow{P}_{R^{1}-X} R \xrightarrow{O}_{R^{1}-X} \xrightarrow{O}_{R^{1}} X \xrightarrow{O}_{R} \xrightarrow{O}_{R^{1}-X} \xrightarrow{O}_{R^{1}-X}$$

Alkylation reactions with unsymmetrical ketones that have essentially the same pK_a for both α -hydrogens often show poor regioselectivity, and over-alkylation can be a problem when reactive alkyl halides are used. Partial equilibration can occur under some reaction conditions, as shown for reactions of **72**, leading to poor regioselectivity.⁶⁸ When LiNH₂ was used as a base in THF, and then quenched with iodobutane, a single alkylation product was obtained in 95% yield (**73**, the kinetic product since equilibration is minimal under these conditions). With excess base and a complexing agent such as HMPA, however, equilibration occurred and alkylation gave a mixture of **73** and **74** (52% and 14% yield, respectively, along with



dialkylation products).⁶⁸ Polyalkylation may be a problem when a very reactive halide such as iodomethane is used under equilibrating conditions. Treatment of cyclohexanone with sodium amide and then iodomethane gave the expected 2-methylcyclohexanone (**75**), but this α -alkyl derivative was deprotonated under the reaction conditions to give **76**, and a second methylation gave **77**. If an excess of iodomethane was present, the tetramethylated cyclohexanone derivative (**78**) was formed. The 2,6-dimethyl and the 2,2,6-trimethylcyclohexanone derivatives are also possible products from this reaction, although it is usually difficult to prepare and isolate, **77** by this method.



Enolates derived from acid derivatives can also be alkylated. Esters, lactones, amides, lactams or carboxylic acids can all be directly alkylated via an enolate anion intermediate. An example is the treatment of lactone **79** with NaH in DMF (NaH can be used because of the enhanced acidity of the 1,3-dicarbonyl moiety in **79**) followed by reaction with an excess of iodomethane

 ⁽a) Binkley, E.S.; Heathcock, C.H. J. Org. Chem. 1975, 40, 2156; (b) for a related reaction, see Stork, G.; Rosen, P.; Goldman, N.L.J. Am. Chem. Soc. 1961, 83, 2965.

to give an 89% yield of **80** as part of Hale and Li's synthesis of (+)-eremantholide.⁶⁹ Note that alkylation proceeded with inversion of configuration.



MOLECULAR MODELING: Stereochemistry of Reactions of Enolates

Examination of an accurate 3D model will often provide sufficient insight into the stereochemistry of the product resulting from attack of an electrophile on an enolate anion. This, of course, assumes that steric factors are the controlling influence. Consider for example, the enolate formed by deprotonation of the polycyclic lactone shown below (see also *homework problem 1*).



First, examine a space-filling model for the enolate anion (left). Is the "convex" or "concave" face more accessible, or are they equally accessible? In other words, when the enolate anion donates electrons to the methyl carbon of MeI, is the methyl group likely to attach to the "top" face of the product, as shown? Does this rule in favor of steric control of the stereochemistry of reaction? Elaborate.

Next, examine a local ionization potential map for the enolate anion (right). This colors an electron density surface which gives the overall molecular size and shape (where a reagent can approach) with the value of the local ionization potential (the energy required to expel an electron from a given location on the surface). By convention, regions on the surface where the ionization potential is small (electrons are loosely bound) are colored "red", while regions where the ionization is large (electrons are tightly bound) are colored "blue". The more loosely bound the electrons, the more likely they are to be donated to an approaching electrophile. In summary, red regions are more likely the target for attack by an electrophile. The map is displayed as a transparent model to allow you to see the structure underneath. Once you become oriented, you can switch to a solid model to allow the colors to be seen more clearly (*click* on the map and select *Solid* from the **Style** menu at the bottom of the screen). Based on the local ionization potential map, what product is favored? Is this the observed product? Is this the same product that is suggested by inspection of the space-filling model? If not, suggest why not.

^{69.} Li, Y.; Hale, K.J. Org. Lett. 2007, 9, 1267.

MOLECULAR MODELING: Selectivity in Methylation of Enolates

Enolate anions react with alkyl halides to give the corresponding alkylated carbonyl derivative. Enolate anions from ketones, aldehydes, esters, lactones, lactams, etc., are all known to undergo reaction with alkyl halides such as iodomethane. Such alkylation reactions are often highly regio and stereoselective. While steric preferences may be obvious from inspection of a 3D model (or even a 2D sketch), other factors may contribute to or even dominate product selection. Here, graphical models such as the local ionization potential map may prove of value. Consider for example, methylation of the enolate anion formed from each of the three bicyclo[4.4.0]decanones, **A-C**. Each leads to a single product.



Examine local ionization potential maps for the three enolate anions for A-C (left to right on screen) and assign the products. These correspond to deprotonation at the carbon substituted with the electron-withdrawing group. (Note that the model for A has been simplified by replacing the OTHP group by hydrogen; this is far removed from the reaction site and should be of little consequence.) These maps show whether electrons are tightly bound ("blue") or loosely bound ("red") as a function of location on an electron density surface (depicting overall molecular size and shape). The smaller (more red) the ionization potential for a region on the map, the more likely it is to donate electrons to the electrophile, so you want to identify the red regions. The maps are displayed as transparent models in order for you to see the structure underneath. Once you are properly oriented, you can switch to solid models, by *clicking* on one of the maps and selecting *Solid* from the Style menu at the bottom of the screen. This will allow you to more easily distinguish subtle differences in the local ionization potential for different regions. You can also "measure" the value of the ionization potential at a particular location on the surface by *clicking* on this location. The value will be displayed at the bottom of the screen. Do some or all the maps reveal a preference for methylation onto one face of the enolate over the other? Which enolate shows the greatest preference and which shows the least? Draw each of the resulting products.

There are two classical reaction sequences in organic chemistry that rely on enolate alkylation. One is the **malonic ester synthesis**.^{70,71} In a synthetic example taken from Sulikowski and co-worker's studies on the biosynthesis of phomoidride B,⁷² di-*tert*-butyl malonate was treated with sodium hydride in the presence of 6-iodo-2(*E*)-hexene to give the alkylated product **81** in >95% yield. In this study, the deuterated acid was the target, and hydrolysis of **81** to the diacid with trifluoroacetic acid was followed by α -deuteration by treatment of the diacid with NaOD in D₂O, giving **82**. Heating **82** in the NaOD/D₂O solution led to decarboxylation as well as

^{70. (}a) Meyer, K.H. Berichte 1912, 45, 2864; (b) Hauser, C.R.; Hudson, Jr., B.E. Org. React. 1942, 1, 266.

^{71. (}a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-57; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 406-407.

^{72.} Sulikowski, G.A.; Agnelli, F.; Spencer, P.; Koomen, J.M.; Russell, D.H. Org. Lett. 2002, 4, 1447.

incorporation of a second α -deuterium, and isolation of 83 in 83% yield from 81.

$$\begin{array}{c} CO_{2}t-Bu \\ CO_{2}t-Bu \end{array} \xrightarrow{NaH, THF} \\ CO_{2}t-Bu \end{array} \xrightarrow{CO_{2}t-Bu} \\ 81 \end{array} \xrightarrow{1. TFA} \\ CO_{2}t-Bu \\ CO_$$

The second classical reaction mentioned above is the **acetoacetic ester synthesis**.^{68b,73} In this sequence, an ester of acetoacetic acid (3-oxobutanoic acid) such as ethyl acetoacetate is treated with base under thermodynamic control conditions and alkylated, as with the malonic ester synthesis. Reaction with sodium ethoxide in ethanol (an ethyl ester is being used) gave the enolate anion, and quenching with benzyl bromide led to **84**. Saponification and decarboxylation gave a substituted ketone (**85**). Although the malonic ester synthesis and the acetoacetic ester synthesis are fundamentally similar, the different substrates lead to formation of either a highly substituted acid or a ketone. The reaction is not restricted to acetoacetate derivatives, and any β -keto-ester can be used.⁷⁴

$$\begin{array}{c} O \\ O \\ CO_2Et \end{array} \xrightarrow{1. \text{ NaOEt, EtOH}} \\ \hline 2. \text{ BnBr} \end{array} \xrightarrow{O} \\ \hline 84 \end{array} \begin{array}{c} O \\ CO_2Et \end{array} \xrightarrow{1. \text{ aq NaOH}} \\ \hline 2. \text{ H}_3O^+ \\ \hline 3. \text{ heat } (-CO_2) \end{array} \xrightarrow{O} \\ \hline 85 \end{array} \begin{array}{c} Ph \end{array}$$

The key to all of these reactions is the enhanced acidity of the hydrogen on the carbon between the two carbonyls. As noted in Table 9.1, 1,3-dicarbonyl derivatives have a pK_a in the range of 8-12 for that proton. The enolate anion formed from a 1,3-dicarbonyl compound is somewhat less reactive because the enolate is more stable due to resonance delocalization. For this reason, higher reaction temperatures are usually (but not always) required. A typical experiment will use the reflux temperature of the alcohol solvent being used. Another alternative is to use a complexing agent such as HMPT or HMPA (see above), or DABCO (diazabicyclo[2.2.2] octane).

Intramolecular cyclization is possible using a doubly activated enolate anion. In the Deslongchamps and co-workers synthesis of (+)-martimol,⁷⁵ keto-ester **86** was treated with the basic cesium carbonate and intramolecular displacement of the allylic chloride gave the macrocycle **87** in 75% yield. There is a related ring-forming process called the **Perkin alicyclic**

^{73. (}a) Krauch, H.; Kunz, W. Organic Name Reactions, John Wiley, New York, 1964, pp 1-2; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-1; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 2-3.

^{74.} Cochrane, J.S.; Hanson, J.R. J. Chem. Soc. Perkin Trans. 1 1972, 361.

^{75.} Toró, A.; Nowak, P.; Deslongchamps, P. J. Am. Chem. Soc. 2000, 122, 4526.

synthesis⁷⁶ (see sec. 9.4.B.i). In general, this useful modification of the malonic ester synthesis condenses an α,ω -dihalide with a malonic ester (although other 1,3-dicarbonyl derivatives can be used). This particular reaction converts malonic acid derivatives to cyclic compounds having a carboxylic acid substituent (cyclopentanecarboxylic acid or cyclohexanecarboxylic acid, for example). Notice that this is an intramolecular alkylation reaction, which is quite common. An example of an intramolecular alkylation reaction that employs a ketone rather than a keto-ester treated **88** with *tert*-butoxide in THF to give a 92% yield of **89**, in Coate's and co-worker's synthesis of cameroonan-7 α -ol.⁷⁷



Variations of the malonic ester and acetoacetic ester sequences lead to many useful synthetic opportunities. In the examples quoted, the base-solvent pair used was ethanol-sodium ethoxide where the alkoxide is the conjugate base of the solvent. If NaOEt–EtOH were used with a methyl ester, transesterification⁷⁸ would give a mixture of methyl and ethyl esters as products. For both malonic ester and acetoacetic ester removal of the most acidic proton (α to both carbonyls) also gives the more thermodynamically stable enolate. Either NaOEt–EtOH or LDA-THF will generate the desired enolate. The malonic ester synthesis is most useful for the synthesis of highly substituted monoacids, and the acetoacetic ester synthesis is used to prepare substituted methyl ketones.

The disconnections for the malonic and acetoacetic ester syntheses are

$$R^{\frown}CO_{2}H \implies R-X + HO_{2}C^{\frown}CO_{2}H \qquad R^{\frown}R^{1} \implies O R^{1} \longrightarrow O R^{1}-X$$

^{76. (}a) Perkin, Jr., W.H. *Berichte* 1883, 16, 1787 (see p 1793); (b) Perkin, Jr., W.H. *J. Chem. Soc.* 1885, 47, 801; (c) van Heyningen, E. *J. Am. Chem. Soc.* 1954, 76, 2241; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-71; (e) and see Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 492-493.

^{77.} Davis, C.E.; Duffy, B.C.; Coates, R.M. J. Org. Chem. 2003, 68, 6935.

 ⁽a) Smith, M.B.; March, J. March's Advanced Organic Chemistry, 6th ed., Wiley, New York, 2007, pp 1419-1421;
 (b) Koskikallio, J. in Patai, S. Ed. The Chemistry of Carboxylic Acids and Esters, Interscience, New York, 1969.

9.3.B. O Versus C Alkylation of Enolate Anions

As discussed in Section 9.2.E, cyclization of **48** gave **50**, via an intramolecular alkylation reaction of enolates. However, vinyl ether 51 was also formed during this reaction, which illustrates an important competing reaction in the alkylation of enolates. An enolate anion is a bidentate nucleophile because it contains two nucleophilic centers, the carbanionic center and the oxygen anion as illustrated by resonance contributors 90. Reaction of the O-nucleophile in 90 with an alkyl halide leads to the vinyl ether 91. Reaction at the C nucleophile of 90 generates the usual alkylation product 92. Since a carbanion is usually more nucleophilic than an alkoxy anion for common electrophiles, 92 tends to be the major product. There are several factors that can influence the relative proportion of these products, however. When 92 is the major product, the process is referred to as C-alkylation and it is greatly preferred in ether solvents when lithium enolates are used. Ether solvents promote the nucleophilic nature of the enolate, favoring the carbanion. The lithium enolate forms a relatively covalent O-Li bond, again favoring C-alkylation. When very reactive halides (iodomethane, allvl bromide) react with sterically unhindered enolates (usually with a potassium or sodium gegenion), O-alkylation (formation of product 91) is preferred. The highly ionic O-Na or O-K bond effectively increases the nucleophilic character of the oxygen. When the alkylation occurs intramolecularly, O-alkylation can be a much more serious problem. Approach of the carbon nucleophile to the electrophilic center is sometimes restricted due to the nature of the tether (see sec. 6.6.A for Baldwin's rules). When the highly polar solvent DMSO is used, the enolate is largely monomeric, which increases reactivity and favors O-alkylation. The product distribution depends on the substitution pattern of the enolate and the nature of the counterion, as in Table 9.6.79



^{79.} Zook, H.D.; Miller, J.A. J. Org. Chem. 1971, 36, 1112.

P	0 h 93	, R ¹ -	O Me ^{. S} ∼M DMSO, 30°C	$Ph \xrightarrow{O^- M^+}_R R^1$	$\frac{R^2X}{30^{\circ}C}$	0 Ph →	R^2 R^2 R^2	• + Ph	$\mathbf{R}^{\mathbf{R}^{1}}_{\mathbf{R}}$
R	R ¹	М	R ² X	95 : 96	R	R <u>1</u>	М	R ² -X	95 : 96
H	 Ph	Na	<i>n</i> -PrCl	1:3.7	Me	Me	Li	<i>i</i> -BuCl	1:1.4
			<i>i</i> -BuCl	1:4.8				<i>n</i> -Amvl Cl	1:0.45
			n-Amyl Cl	1:3.6					
			<i>n</i> -Amyl Br	1:7.1			Na	<i>n</i> -PrCl	1:0.77
	T.	. .		1 0 0				<i>i</i> -BuCl	1:1.5
н	Et	Lı	n-PrCl	1:0.9				<i>n</i> -Amyl Cl	1:0.48
			<i>n</i> -PrBr	1:2.3	Et	Et	Na	n-PrCl	1:0.14
			<i>i</i> -BuCi	1.1.9				<i>i</i> -BuCl	1:0.28
			<i>n</i> -Amyl Cl	1.0.77				n-Amyl Cl	1:0.11
			<i>n</i> -Amyl Br	1.1.2	DI	Ы	. .		1 -0.01
			<i>n</i> -Amyri	1.5	Pn	Pn	L1	<i>n</i> -PrCl	1:<0.01
		Na	n-PrCl	1:0.77				<i>n</i> -Amyl Cl	1:<0.01
			i-BuCl	1:1.9					
			n-Amyl Cl	1:0.8					
			<i>n</i> -Amyl Br	1:1.6					
			<i>n</i> -Amyl I	1:4.4					
		Cs	<i>n</i> -Amyl Cl	1:0.77					
[Reprin Americ	[Reprinted with permission from Zook, H.D.; Miller, J.A. J. Org. Chem. 1971, 36, 1112. Copyright © 1971 American Chemical Society.]								

 Table 9.6.
 O- Versus C-Alkylation for Phenyl Ketones in DMSO

Treatment of ketone **93** with dimsyl anion generates enolate **94**, but this enolate anion can potentially form a mixture of (*E*)- and (*Z*)-isomers. Reaction of **94** with various alkyl halides led to the *O*-alkylation product (**95**) and the *C*-alkylation product (**96**). In DMSO, the ratio of *O*- to *C*-alkylation is relatively insensitive to changes in the gegenion (the metal), suggesting that the enolate is an unencumbered anion in this cation solvating medium. Note that *C*-alkylation is preferred except when the steric bulk at the nucleophilic carbon becomes too great (R, R¹ = Ph, Ph or Et, Et). For PhCOCHPh₂ (**93**, R¹ = R² = Ph), *O*-alkylation is effectively the only process.

Enolate anions react with acyl halides or anhydrides to give the acylated product. Both *C*-acylation and *O*-acylation are possible. In general *O*-acylation predominates⁸⁰ (section 9.3.C). If *C*-acylation is desired, the acyl unit must be modified. One solution is to use acyl cyanides. In an example taken from Nicolaou and co-worker's synthesis of coleophomone $B_{,81}^{,81}$ acyl cyanide **98** was prepared from aldehyde **97** by treatment with Et₂AlCN (**Nagata's reagent**)⁸² followed by oxidation of the resulting alcohol with PCC. When **98** was treated with

^{80.} See Krapcho, A.P.; Diamanti, J.; Cayen, C.; Bingham, R. Org. Synth. Coll. Vol. V 1973, 198.

^{81.} Nicolaou, K.C.; Vassilikogiannakis, G.; Montagnon, T. Angew. Chem. Int. Ed. 2002, 41, 3276.

^{82.} Nagata, W.; Yoshioka, M.; Murakami, M. Org. Synth. Coll. Vol. VI 1988, 307.

5-methyl-1,3-cyclohexanedione and triethylamine, C-acylation proceeded smoothly to give **99** in 98% yield.



This type of reaction can sometimes be useful in synthesis, but the structural units on the substrate influence *C*- versus *O*- reactivity. In the Honda et al. formal synthesis of securinine,⁸³ *N*-benzylamino ketone (**100**) was treated with lithium hexamethyldisilazide and then sorbic anhydride. This sequence gave dienyl ester **101** by *O*-alkylation of the initially formed enolate anion. When the nitrogen-protecting group was changed to *N*-Boc (see **102**), however, the identical reaction gave *C*-acylation and the product was **103**. Neither of these products was suitable for the synthesis, but the reaction with 2-acetyl pyridine (**104**) gave **105**, which was transformed into securinine. This example shows that *O*- versus *C*-acylation is very dependent on the local environment and electronic effects within the enolate anion.



The synthesis of (+)- and (–)-saudin by Boeckman and co-worker's⁸⁴ employed an interesting variation that involved *O*-alkylation. Treatment of **106** with potassium hexamethyldisilazide removed a proton from the distal methyl group (acidic due to vinylogy caused by the conjugated enone system), and subsequent reaction with the triflate shown gave enol ether **107** in good yield. Apart from the use of a vinylogous enolate anion, this example illustrates that triflates also give *O*-alkylated product.

^{83.} Honda, T.; Namiki, H.; Kudoh, M.; Watanabe, N.; Nagase, H.; Mizutani, H. Tetrahedron Lett. 2000, 41, 5927.

^{84.} Boeckman Jr., R.K.; Ferreira, M.d R.R.; Mitchell, L.H.; Shao, P. J. Am. Chem. Soc. 2002, 124, 190.

$$O = \underbrace{CO_2Me}_{106} \xrightarrow{1. \text{ KHMDS, THF-HMPA, }-78^\circ\text{C}}_{2. -78^\circ\text{C}, \text{ OTf}} \xrightarrow{OSiPh_2t-Bu}_{O} \xrightarrow{OSiP$$

To put this problem into perspective, when ether or THF are used as the solvent, *O*-alkylation is a much less serious problem in reactions with alkyl halides. With the possible exception of iodomethane, the use of lithium enolates in ether solvents leads to *C*-alkylation as the major product in virtually all cases. When the enolate carbanion center is sterically hindered, *O*-alkylation can be a problem even in THF or ether. Some reagents such as silyl halides and anhydrides show a preference for *O*-alkylation. Both of these *O*-alkylation reactions will be discussed in Section 9.3.C.

9.3.C. Enolate Reactions with Non-Carbonyl Electrophiles

Enolate anions react with many electrophilic species other than alkyl halides, analogous to the reactions of other carbanions (Chap. 8). Nucleophilic ring opening of an epoxide to give alcohols is very common,⁸⁵ occurring at the less sterically hindered carbon. Grieco et al. reacted the dilithio salt of acetic acid (LiCH₂CO₂Li, sec. 9.4.B.vii) with epoxide **108** to give **109**,

in a synthesis of bigelovin.⁸⁶ The regioselectivity in the ring opening is probably due to a combination of neighboring group effects with the adjacent hydroxyl group, and steric blocking of one carbon by the bridgehead methyl.



The epoxide ring opening gives the interesting disconnection,

$$R \xrightarrow{OH}_{R} \xrightarrow{O}_{X} \xrightarrow{O}_{X} \xrightarrow{O}_{X} + \xrightarrow{O}_{R} \xrightarrow{O}_{R} \xrightarrow{R}$$

It is also possible to oxygenate an enolate to give the corresponding acyloin (an α -hydroxy ketone) or alkoxy derivative. In Danishefsky and co-worker's synthesis of myrocin C,⁸⁷ reaction of an enol ether such as **110** with 3,3-dimethyldioxirane (DMDO) gave the protected α -hydroxy ketone (**111**). Reaction of an enolate anion with oxygen and trimethylphosphite [(MeO)₃P] gives an α -hydroxy derivative.⁸⁸ MoOPh is an effective oxygenation reagent for

^{85.} For a review of such reactions, see Taylor, S.K. Tetrahedron 2000, 56, 1149.

^{86.} Grieco, P.A.; Ohfune, Y.; Majetich, G. J. Org. Chem. 1979, 44, 3092.

^{87.} Chu-Moyer, M.Y.; Danishefsky, S.J.; Schulte, G.K. J. Am. Chem. Soc. 1994, 116, 11213.

^{88.} For an example taken from a synthesis of brefeldin A, see Corey, E.J.; Wollenberg, R.H.; Williams, D.R. *Tetrahedron Lett.* **1977**, 2243.

enolate anions, and it can be used with enolate anions of several different carbonyl compounds. In a synthetic work towards the trichodermamides A and B, Joullié and co-workers treated lactone **112** with potassium hexamethyldisilazide and then MoOPh to give **113** in 70% yield.⁸⁹ The actual structure of MoOPh is MoO₅•Py•HMPA.⁹⁰ Nozoe and co-workers showed that 2-phenyl-2-*p*-toluene-sulfonyloxazidine (sec. 3.9.A.ii) could convert the enolate derived from a 2-pyrrolidinone derivative to the 3-hydroxy derivative (α -hydroxylation) in good yield.⁹¹ Another reagent that reacts with enolate anions to generate α -hydroxy ketones is the **Davis reagent** (2-phenylsulfonyl-3-phenyl-oxaziridine).⁹² A variety of enolate anions, including those derived from carboxylic acid derivatives, can be hydroxylated in this manner. In a synthesis of jiadifenin by Danishefsky and co-workers, the lactone enolate anion generated from sodium hexamethyldisilazide and lactone **114** was treated with the Davis reagent to give a 42% yield of α -hydroxy lactone **115**.⁹³



Enolates react with sulfenyl halides to give an α -alkylthio ketone. As shown for cyclohexanone, reaction with LDA followed benzenesulfenyl chloride (PhSCl) produced phenylthio derivative **116**. The α -proton adjacent to both the carbonyl and the sulfur was more acidic, and deprotonation with potassium hydride gave the enolate. Subsequent alkylation with iodobutane gave a 91% yield of **117**.⁹⁴ As mentioned in Chapter 2, the sulfide moiety can be oxidized to a sulfoxide and thermally eliminated (syn elimination, sec. 2.9.C.v) to give an alkene.⁹⁵ Similar

- (a) Mimoun, H.; Seree de Roch, L.; Sajus, L. Bull. Soc. Chim. Fr. 1969, 1481; (b) Regen, S.L.; Whitesides, G.M. J. Organomet. Chem. 1973, 59, 293.
- 91. Ohta, T.; Hosoi, A.; Nozoe, S. Tetrahedron Lett. 1988, 29, 329.
- 92. (a) Davis, F.A.; Chen, B.-C. Chem. Rev. 1992, 92, 919. (b) Also see Nagasaka, T.; Imai, T. Chem. Pharm. Bull. 1995, 43, 1081; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, p. 755.
- 93. Cho, Y.S.; Carcache, D.A.; Tian, Y.; Li, Y.-M.; Danishefsky, S.J. J. Am. Chem. Soc. 2004, 126, 14358.
- 94. See Coates, R.M.; Pigott, H.D.; Ollinger, J. Tetrahedron Lett. 1974, 3955.
- (a) Trost, B.M.; Salzmann, T.N. J. Org. Chem. 1975, 40, 148; (b) Grieco, P.A.; Reap, J.J. Tetrahedron Lett. 1974, 1097.

Wan, X.; Doridot, G.; Joullie, M.M. Org. Lett. 2007, 9, 977. Also see Vedejs, E. J. Am. Chem. Soc. 1974, 96, 5944.

methodology can be applied to formation and syn-elimination of the corresponding selenides, $-CO-CH(R)-Se-R^{1.96}$



In addition to the methods described for controlling the ratio of thermodynamic and kinetic products, other techniques have been developed to trap the enolate based on reactions with reagents that prefer *O*-alkylation. Reaction of a ketone with acetic anhydride, usually in the presence of a catalytic amount of perchloric acid, generates the thermodynamic enol acetate **118**.⁹⁷ When **118** was treated with methyllithium, acyl addition to the acetyl group led to the thermodynamic enolate (**76**) in high yield. Once available, **76** was treated with an alkyl halide or a carbonyl derivative in the usual manner. Some isomerization occurs on treatment with methyllithium, but the major product of this process is that resulting from alkylation of the thermodynamic enolate.



Trialkylsilyl halides show a great propensity to react with the oxygen rather than the carbon of enolate anions. Stork and Hudrlik showed that enolates can be trapped as the trialkylsilyl enol ether via *O*-alkylation, which is most useful for kinetic enolates in which a lithium enolate (such as the kinetic enolate derived from 2-methyl-cyclohexanone and LDA) is reacted with trimethylsilyl chloride to give an isolable intermediate, **119**.⁹⁸ The enolate is trapped with high efficiency, and conversion to the enolate is readily accomplished by treatment with methyllithium to generate kinetic enolate **120** and the volatile trimethylsilane (Me₃SiH).⁹⁹ This latter reaction is subject to some equilibration, but gives the kinetic alkylation product in good yield. *O*-Silyl enolates¹⁰⁰ can be generated by other reagents, reacting with a variety of starting materials. With kinetic enolates, the trapping procedure is especially useful since the isomeric silyl enol ethers can be isolated and separated from amine by-products and unreacted ketone. Unmasking and alkylation can be accomplished under controlled conditions that minimize equilibration, maximizing the yield of kinetic product.

^{96. (}a) Grieco, P.A.; Miyashita, M. J. Org. Chem. 1974, 39, 120; (b) Reich, H.J.; Renga, J.M.; Reich, I.L J. Org. Chem. 1974, 39, 2133.

 ⁽a) House, H.O.; Kramar, V. J. Org. Chem. 1963, 28, 3362; (b) House, H.O.; Phillips, W.V.; VanDerveer, D. Ibid. 1979, 44, 2400.

^{98.} Stork, G.; Hudrlik, P.F. J. Am. Chem. Soc. 1968, 90, 4464, 4462.

^{99.} House, H.O.; Czuba, L.J.; Gall, M.; Olmstead, H.D. J. Org. Chem. 1969, 34, 2324.

^{100.} Rasmussen, J.K. Synthesis 1977, 91.



9.4. ENOLATE CONDENSATION REACTIONS

The condensation reaction of enolate anions and carbonyl derivatives is one of the most useful in organic chemistry. The condensation is nothing more than an acyl addition reaction of the nucleophilic enolate to an electrophilic carbonyl carbon.¹⁰¹ The generalized reaction is

represented by enolate **121** reacting with carbonyl derivative **122** (an aldehyde or a ketone in this case) to give the acyl addition product **123**. The reaction is straightforward unless R^1 and/or R^2 are very large. Acyl addition may also be slow if R^3 and/or R^4 in the



carbonyl partner are large. If the carbonyl is an aldehyde or a ketone, the reaction gives **123**. If **122** is an acid derivative, however, R^3 or R^4 is a leaving group (Cl, O₂CR, OR, NR₂) and **123** reacts further to produce a 1,3-dicarbonyl compound via acyl substitution (sec. 9.4.B). There are many synthetic variations, and to further complicate matters the enolate may be generated under kinetic or thermodynamic conditions. The more common variations of this reaction are well known, and usually have a name associated with them (i.e. named reactions).^{102,103,104,105}

9.4.A. The Aldol Condensation¹⁰⁶

9.4.A.i. Intermolecular Reactions. The **aldol condensation**¹⁰⁷ is one of the classical reactions of Organic chemistry, apparently first reported by Chiozza in 1856^{107a} and later expanded by

^{101.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd ed., Wiley-VCH, New York, **1999**, pp. 1317-1324.

^{102.} The Merck Index, 14th Edition, Merck and Co, Inc., Whitehouse, New Jersey, 2006, pp ONR-1-ONR-105.

Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005.

^{104.} Krauch, H.; Kunz, W. Organic Name Reactions, John Wiley, New York, 1964.

^{105.} Surrey, A.R. Name Reactions in Organic Chemistry, 2nd Ed., Academic Press, New York, 1961.

^{106. (}a) *Modern Aldol Reactions*, Mahrwald, R. (Ed.), Wiley, NY, *2004*; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, *2006*, p ONR-1; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, *2005*, pp. 26-27.

^{107. (}a) Chiozza, L. Annalen 1856, 97, 350; (b) Wurtz, A. Compt. Rend. 1872, 74, 1361; (c) Perkin, W. Berichte, 1882, 15, 2802; (d) Nielsen, A.T.; Houlihan, W.J. Org. React. 1968, 16, 1; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 8-9; (f) Reference 104, pp 6-10.

Wurtz^{107b} and by Perkin.^{107c} In its earliest version, an aldehyde was mixed with a base and an aldehyde that did not contain an enolizable hydrogen (such as benzaldehyde), under what we now categorize as thermodynamic conditions. Ketones were also used. If acetophenone reacted with benzaldehyde in the presence of sodium ethoxide (in ethanol), the initial product was alkoxide **124**. Hydrolysis provided the β -hydroxy ketone product (an aldol or aldolate) **125**. In general, the hydrolysis step provides the aldolate, but sometimes elimination of water (dehydration) accompanies the hydrolysis to give a conjugated ketone (**126**). Note that heating is usually required to induce dehydration unless there is a conjugating substituent. When an aromatic aldehyde (such as benzaldehyde) is the reaction partner, the aqueous acid workup almost always leads to elimination of water from the aldol product. If an aliphatic aldehyde is used, the aldol product is usually easy to isolate. When an aromatic aldehyde is condensed with an enolate of an aliphatic aldehyde or ketone to give the α , β -unsaturated compound, the reaction is called the **Claisen-Schmidt reaction**.^{108,107d} Note that the aldol condensation can be done using high-intensity ultrasound,¹⁰⁹ where good yields of aldol products were isolated that normally give significant elimination under non-ultrasound conditions.



A major drawback of the reaction as originally formulated is self-condensation. The enolate derived from 3-pentanone (see 127) exists in equilibrium with the ketone under these conditions, and benzaldehyde is present. Enolate 127 can react with benzaldehyde to give the aldolate product 128, and hydrolysis gives the alcohol as a mixture of diastereomers 129 and 130. At this point, we cannot predict one or the other as a major product. For the time being, we will assume that the reaction produces close to a 1:1 mixture of the two products. If this mixture is heated, conjugated ketone 131 is formed. The problem with this approach is clear when we recognize that enolate 127 can also react with unenolized 3-pentanone to produce the self-condensation aldol product (132), and hydrolysis gives 133. Therefore, this reaction could produce three different aldol products.

 ^{108. (}a) Claisen, L.; Claparède, A. *Berichte, 1881, 14*, 2460; (b) Schmidt, J.G. *Ibid. 1881, 14*, 1459; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, *2006*, p ONR-18.

^{109.} Cravotto, G.; Demetri, A.; Nano, G.M.; Palmisano, G.; Penoni, A.; Tagliapietra, S. Eur. J. Org. Chem. 2003, 4438.



This latter point is one disadvantage of the traditional aldol condensation, but there are also advantages. The main advantage is the construction of a relatively complex carbon skeleton from simple precursors. In addition, this carbon-carbon bond forming reaction generates new stereogenic (but racemic) centers. As will be seen in Section 9.5.A, good-to-excellent diastereoselectivity is possible in many cases. The reaction conditions used for the aldol condensation of 3-pentanone described above are rather harsh, and this is a disadvantage if elimination of water from the aldol product occurs, or if self-condensation occurs under these equilibrating conditions. Aldehydes that do not contain an enolizable proton can be added to the enolate of a ketone to give a cross-coupling product, but a large excess of the aldehyde is required to minimize self-condensation.

A crossed-aldol condensation is often desirable between two reactive partners that have an enolizable position, as in 3-pentanone with cyclopentanone. If 3-pentanone and benzaldehyde, which has no enolizable protons, can lead to three products, what will happen in this new case? If an aldol condensation occurs under thermodynamic conditions, 3-pentanone reacts with sodium ethoxide to give enolate **127**. This enolate can condense with either unenolized 3-pentanone (to produce **133**) or with unenolized cyclopentanone (to produce **135**). Both of these ketones are symmetrical, and there is no opportunity for additional enolates, which would further complicate the reaction (see below). The pK_a of 3-pentanone and cyclopentanone are close. Under equilibrium conditions, both enolate anions (**127** and **134**) will be formed, and will be available for reaction. In addition to the formation of **133** and **135**, enolate anion **134** can condense with either the unenolized 3-pentanone (to produce **137**), giving a total of four aldol products in this reaction. Diastereomers are possible for **133** and **135**, increasing the actual number of products. The low yield of the desired aldolate, and problems associated with separation and isolation make this reaction unattractive. Even if one aldolate is produced with some selectivity, the problems

of poor yields and isolation of the desired product remain. It is clear that this mixed aldol condensation is not a synthetically useful reaction as described above.



If an unsymmetrical ketone is used in this reaction, the problem is exacerbated. Reaction of **43** with sodium ethoxide, under thermodynamic control conditions, generates two different enolate anions. When reacted with an aldehyde with no α -hydrogens (benzaldehyde), two aldol products are formed (**138** and **139**) if there is no self-condensation of **43**. When **43** reacted with sodium ethoxide under thermodynamic conditions in the presence of an unsymmetrical ketone such as 2-butanone, the kinetic and thermodynamic enolates of both ketones were formed, so four different enolate anions are formed and each one reacts with two different ketones. Therefore, the attempted mixed aldol condensation of 2-butanone and **43** can produce eight different aldolate products.



One solution to this problem lies in changing from thermodynamic cto kinetic control conditions. If 3-pentanone, for example, were treated with LDA in THF at -78° C, enolate **127** would be produced as the major enolate anion and in high yield. In a subsequent step, cyclopentanone (or **43**) could be added to give a single aldol condensation product. The advantage of kinetic control is the formation of primarily one enolate anion under non-equilibrating conditions, which minimizes self-condensation

products. A kinetically controlled mixed aldol condensation is the reaction of 2-pentanone with LDA and subsequent



condensation with butanal, which gave **140** as the major product.¹¹⁰ If the thermodynamic aldolate is desired, the thermodynamic enolate must be trapped as the enol acetate (see above) and then treated with a carbonyl compound after unmasking with methyllithium.

There are countless synthetic examples of the aldol condensation. In the Perkins and Lister synthesis of dolabriferol¹¹¹ treated the ethyl ketone unit in **141** with an excess of LDA to generate the enolate anion. Subsequent addition of aldehyde **142** gave a 78% yield of aldolate product **143** with 85% ds. Enantioselective¹¹² aldol condensation reactions have been reported. An enantioselective crossed-aldol reaction of aldehydes has been reported. In work by MacMillan and Northrup,¹¹³ *L*-proline was used as a chiral base. The cross-coupling of propanal with cyclohexanecarboxaldehyde, for example, gave an 87% yield of **144** as a 14:1 *anti:syn* mixture, and the *anti*-diastereomer was obtained in 99% enantiomeric purity.



Aldol condensation reactions can be done under acidic conditions. In a synthesis of the immunosuppressant FR901483 by Fukuyama and co-workers,¹¹⁴ keto-aldehyde **145** was treated with camphorsulfonic acid in refluxing benzene, and subsequent protonation of the aldehyde led to the protonated intermediate in the presence of the enol form of the ketone (see **146**). Reaction of the enol with the protonated aldehyde via an intramolecular aldol cyclization (also see Sec. 9.4.A.ii), produced aldolate product **147**, and loss of the proton gave an excellent yield of alcohol **148** with high selectivity.

^{110. (}a) Stork, G.; Kraus, G.A.; Garcia, G.A. J. Org. Chem. 1974, 39, 3459; (b) Gaudema, M. C.R. Acad. Sci. Ser. C 1974, 279, 961.

^{111.} Lister, T.; Perkins, M.V. Org. Lett. 2006, 8, 1827.

⁽a) Cordova, A.; Notz, W.; Barbas III, C.F. J. Org. Chem. 2002 67, 301; (b) List, B.; Pojarliev, P.; Castello, C. Org. Lett, 2001, 3, 573; (c) Yoskikawa, N.; Kumagai, N.; Matsunaga, S.; Moll, G.; Oshima, T.; Suzuki, T.; Shibasaki, M. J. Am. Chem. Soc. 2001, 123, 2466; (d) Trost, B.M.; Silcoff, E.R.; Ito, H. Org. Lett. 2001, 3, 2497.

^{113.} Northrup, A.B.; MacMillan, D.W.C. J. Am. Chem. Soc. 2002, 124, 6798.

^{114.} Kan, T.; Fujimoto, T.; Ieda, S.; Asoh, Y.; Kitaoka, H.; Fukuyama, T. Org. Lett. 2004, 6, 2729.



Lewis acids also catalyze the aldol condensation. In presence of a catalytic amount of TiCl₄,¹¹⁵ 2-butanone was condensed with benzaldehyde in toluene to give an 83% yield of the aldolate product. Under these conditions, the reaction was highly regioselective for the thermodynamic product. In another example, taken from the synthesis of siphonarin B by Patterson and co-workers,¹¹⁶ aldehyde **149** was condensed with ketone **150** in the presence of Sn(OTf)₂ to give a 92% yield of **151**. The aldolate product formed diastereoselectively, generating a 2.7:1 mixture of syn,syn:(syn,anti + anti,anti) diastereomers.



Nevalainen and Simpura reported another variation of this classic reaction called the aldoltransfer reaction. In the presence of a suitable catalyst, usually an aluminum compound, an aldolate product reacts with an aldehyde to give a ketone and a new aldolate.¹¹⁷ An example is the reaction of benzaldehyde with aldolate **152** in the presence of 5% of aluminum catalyst (**153**). In dichloromethane at ambient temperature, a 62% yield of aldolate **154** was obtained after a reaction time of 43 h. The other product of this reaction was acetone, which was readily removed. This transformation involves a retro-aldol reaction of **152** (see sec. 9.5.A.vi.) and the resultant enolate anion reacts with benzaldehyde. Several aldehydes were used and **152** is particularly attractive (the aldol condensation product of acetone) because acetone is the second product.



^{115.} Mahrwald, R.; Gündogan, B. J. Am. Chem. Soc. 1998, 120, 413.

^{116.} Paterson, I.; Chen, D.Y.-K.; Franklin, A.S. Org. Lett. 2002, 4, 391.

^{117.} Simpura, I.; Nevalainen, V. Angew. Chem. Int. Ed. 2000, 39, 3422.

The aldol disconnection is

9.4.A.ii. Intramolecular Reactions. The intramolecular aldol condensation is particularly useful, and is illustrated by the simple reaction of 2,5-hexanedione with LDA to first give kinetic enolate **155**. This enolate could condense with a second molecule of dione to give an aldolate product, but intramolecular attack of the second carbonyl group is much faster and leads to the cyclic aldolate product **156**, which gives **157** upon hydrolysis. In Skrirsihna and Ramasastry's synthesis of (+)-2 β -hydroxysolanascone,¹¹⁸ intramolecular aldol condensation of **158** with piperidine as the base gave a 90% yield of **159**. The course of the intramolecular aldol condensation can be influenced by steric and conformational factors, as well as the rate of competing cyclization reactions. In a synthesis of (+)-dichroanone by Stoltz and McFadden,¹¹⁹ diketone **160** was heated with excess KOH in xylenes, using a Dean-Stark trap to remove water, and the resulting intramolecular aldol condensation led to **161** in 80% yield. Note that water was eliminated upon workup.



Another example illustrates some the problems inherent in the intramolecular reaction that do not arise with the intermolecular version. Deprotonation of 162 with sodium ethoxide under thermodynamic control conditions gave enolate anion 163 and isolated product 167 (water was lost from the initial aldolate product), which was used in Rouessac and Alexandre's

^{118.} Srikrishna, A.; Ramasastry, S.S.V. Tetrahedron Lett. 2006, 47, 335.

^{119.} McFadden, R.M.; Stoltz, B.M. J. Am. Chem. Soc. 2006, 128 7738.

synthesis of isoshyobunone.¹²⁰ Under these reaction conditions, four different enolate anions (**163** and **168-170**) are possible via **162**. The intramolecular aldol condensation reaction with **168** and **170** would generate four-membered rings, which is energetically less favorable (secs. 1.5.B, 6.6.B) than formation of the six-membered rings that can be formed from the other enolates, **169** and **163**. Another product was formed in the enolate condensation reaction of **162**, dienone **167**, the kinetic product, relative to cyclization via **169**. When enolate **163** closed to form **164**, hydrolysis generated the aldolate **165**. Dehydration gave the ketone with the C=C unit conjugated to the carbonyl group (**166**), but the isopropenyl double bond remained out of conjugation. Under the acidic conditions of the workup, that double bond moved into conjugation to give the final product **167**. Despite several possible reaction pathways, this intramolecular aldol cyclization proceeded with high selectivity for a single product. The cyclization is governed by the factors discussed in section 6.6 for ring closures, which poses problems not encountered with the intermolecular aldol condensation.



The disconnection for an intramolecular aldol condensation is:



9.4.B. Condensation Reactions of Acid Derivatives

Just as ketone and aldehyde enolates react with ketones and aldehydes, they can also react with esters and other acid derivatives.¹²¹ Similarly, esters and other acid derivatives can be converted to their enolate anions, and then react with another acid derivative, or with an aldehyde or ketone. There are many variations of this reaction. When an acid derivative is attacked by a nucleophile, the alkoxide product contains a leaving group and this leads to acyl

^{120. (}a)Alexandre, C.; Rouessac, F.J. Chem. Soc. Chem. Commun. 1975, 275; (b)Idem Bull. Chim. Soc. Fr. 1977, 117.

^{121.} For reactions of this type, and related reactions, see Larock, R.C. *Comprehensive Organic Transformations,* 2nd ed., Wiley-VCH, New York, **1999**, pp 1528-1546.

substitution as described for reactions of acid derivatives and Grignard reagents (sec. 8.4.C.ii) and organolithium reagents (sec. 8.5.E). This chemistry is summarized by the conversion of carbonyl derivative **171** to the enolate (**172**), and subsequent reaction with an acid derivative (**173**). Attack at the acyl carbon produces the usual alkoxide (**174**), but the X group is a leaving group (Cl, O_2CR , OR, NR_2) and expulsion of X leads to a 1,3-dicarbonyl compound **175**. This is, of course, the normal acyl substitution sequence. This section will examine those reactions where the carbonyl partner is an acid derivative and, in many cases, the enolate partner will also be an acid derivative. Esters, lactones, anhydrides, amides or lactams can be used as the enolate anion precursor, reacting with aldehydes, ketones or esters. Both intermolecular and intramolecular reactions are known. The remainder of this section will focus on a variety of carbonyl enolate precursors. To illustrate that virtually all acid derivatives can be used in this reaction, amide **176** was treated with LDA, and intramolecular condensation with the ketone unit gave a 92% yield of lactam-alcohol **177**, in McWhorter and Liu's synthesis of 8-desbromohinckdentine A.¹²²



9.4.B.i. The Claisen Condensation. A classical reaction is the condensation of an ester enolate with an ester, illustrated by the self-condensation of ethyl butanoate in the presence of sodium ethoxide to give β -keto-ester 180. Initial reaction with the base under thermodynamic control in this case, generated the enolate anion (178). This anion attacked the carbonyl of a second molecule of ethyl butanoate to give the tetrahedral intermediate 179. Displacement of ethoxide generated ketone 180. As shown here, this reaction is known as the Claisen condensation.¹²³

^{122.} Liu, Y.; McWhorter Jr., W.W. J. Am. Chem. Soc. 2003, 125, 4240.

^{123. (}a) Hellon, R.; Oppenheim, A. Berichte, 1877, 10, 699; (b) Israel, A. Annalen 1855, 231, 197; (c) Claisen, L. Berichte, 1887, 20, 655; (d) Beyer, C.; Claisen, L. Ibid. 1887, 20, 2178; (e) Claisen, L.; Stylos, N. Ibid. 1887, 20, 2188; (f) Claisen, L. Annalen 1894, 281, 306; (g) Reference 104, pp 94-96; (h) Reference 105, pp 49-51; (i) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-18; (j) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 150-151.



The reaction described for ethyl butanoate is a self-condensation, but as with the aldol condensation. Claisen condensation of two different esters can result in a mixture of products under thermodynamic control conditions. The reaction of two different esters is called the crossed-Claisen (or a mixed Claisen) condensation. A generalized reaction involving RCO₂Et and R¹CO₂Et can lead to at least four different condensation products. One ester (RCO₂Et) can condense with itself to give 181 or with R^1CO_2Et to give 182. Similarly, ester R^1CO_2Et



can condense with itself to give 183, or product is desired. A synthetic example is

taken from Panek and co-worker's synthesis of leucascandrolide A,¹²⁴ in which the lithium enolate anion of *tert*-butyl acetate reacted with β -epoxy ester **185** in THF, to give a 70% yield of 186. Self-condensation of the lithium enolate with the parent ester is sometimes a problem when LDA is used as a base,¹²⁵ but using the *tert*-butyl ester or LICA minimizes this competing process.¹²⁶ In general, forming the ester enolate under kinetic control conditions gives greater flexibility in the condensation, allowing the lithium enolate to be condensed with a variety of other esters (as in formation of 186). It is noted that a full equivalent of base is required to form the enolate anion. The Claisen condensation can be used in incorporate an aldehyde unit into a molecule. In Padwa and Danca's synthesis of jamtine,¹²⁷ ester 187 was treated with LDA to form the enolate anion, and subsequent reaction with ethyl formate gave aldehyde 188 via the acvl substitution reaction.



The α -proton in a normal Claisen product is more acidic than in the starting ester since it is adjacent to two carbonyls (see Table 9.1). Reaction with base under thermodynamic conditions

127. Padwa, A.; Danca, M.D. Org. Lett. 2002, 4, 715.

^{124.} Su. O.: Dakin, L.A.: Panek, J.S. J. Org. Chem. 2007. 72. 2.

^{125. (}a) Rathke, M.W.; Sullivan, D.F. J. Am. Chem. Soc. 1973, 95, 3050; (b) Lochmann, L.; Lím, D. J. Organomet. Chem. 1973, 50, 9; (c) Sullivan, D.F.; Woodbury, R.P.; Rathke, M.W. J. Org. Chem. 1977, 42, 2038.

^{126.} Rathke, M.W.; Lindert, A. J. Am. Chem. Soc. 1971, 93, 2318.

will give the 1,3-dicarbonyl enolate, where deprotonation of a product such as **186** is certain. The resulting anion is relatively stable, however, due to the increased resonance delocalization possible when two carbonyl groups are present (sec. 9.2.A). This means that the product enolate is *less reactive* than the enolate derived from the ester starting material, and generally does not give significant amounts of condensation product. The thermodynamic conditions that employ an alkoxide base require that the alcohol solvent be the conjugate acid of that base (methanol with sodium methoxide, for example), or transesterification will give two different esters for all products.

There are two important variations of this condensation. In the first, an ester enolate is condensed with a ketone or aldehyde. This has been called the **Claisen reaction**.¹²⁸ Pons and co-worker's synthesis of goniothalamin¹²⁹ condensed ethyl acetate with cinnamaldehyde to give an 85% yield of **189**. When the reaction is modified to use an aldehyde or ketone enolate rather than an ester enolate but the reactive partner is an ester, it is still referred to as the **Claisen reaction**. In this variant, a ketone or aldehyde enolate reacts with an ester to give a 1,3-diketone. In the Hua et al. synthesis of tetrahydro-1-oxpyranobenzopyrans, the dianion of **190** was condensed with ethyl pyridine-3-carboxylate gave an 88% yield of **191**,¹³⁰ which exists largely in the enol form shown.



Reaction of an ester enolate with an acid chloride will also generate a β -keto-ester and is a useful alternative to the Claisen condensation. Ketone enolates can also be condensed with acid chlorides.¹³¹ An ester enolate can be trapped with trimethylsilyl chloride, as with aldehydes and ketones. An interesting variation of this condensation involved lactone **192**, which was condensed with a lithio-acetate (R = *t*-Bu, Et) in a modified Claisen condensation to give **193**.¹³² Rather than the normal loss of alkoxide to give the β -diketone, **193** was hydrolyzed under mild conditions to give alkoxy hydroxy-ester **194**.

^{128.} Claisen, L. Berichte, 1890, 23, 976.

^{129.} Fournier, L.; Kocienski, P.; Pons, J.-M. Tetrahedron 2004, 60, 1659.

Hua, D.H.; Chen, Y.; Sin, H.-S.; Maroto, M.J.; Robinson, P.D.; Newell, S.W.; Perchellet, E.M.; Ladesich, J.B.; Freeman, J.A.; Perchellet, J.-P.; Chiang, P.K. J. Org. Chem. 1997, 62, 6888.

^{131.} Beck, A.K.; Hoekstra, M.S.; Seebach, D. Tetrahedron Lett. 1977, 1187.

^{132.} Duggan, A.J.; Adams, M.A.; Brynes, P.J.; Meinwald, J. Tetrahedron Lett. 1978, 4323.

The Claisen disconnection is

A variation of this condensation involves reaction with aldehydes, and it is called the **Perkin** reaction¹³³ (also see sec. 9.3.A). Condensation of an aldehyde (having no enolizable protons) with the enolate of an acid anhydride leads to an acetoxy ester such as 195.^{133a} Internal acyl substitution by the alkoxide forms the *O*-acetyl ester and liberates the carboxylate anion (196). Subsequent reaction with more acetic anhydride generates a new mixed anhydride 197. Saponification leads to the β -hydroxy acid, which eliminates water in the acid hydrolysis step to give the final product, the aryl acrylic acid derivative (198, cinnamic acid).



The Perkin disconnection is



9.4.B.ii. The Dieckmann Condensation. Just as there is an intramolecular version of the aldol condensation, there is an intramolecular version of the Claisen condensation but it has

^{133. (}a) Perkin, W.H. J. Chem. Soc. 1869, 21, 53, 181; (b) Johnson, J.R. Org. React. 1942, 1, 210; (c) Reference 104, pp. 344-346; (d) Reference 105, pp 184-186; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-71; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 492-493.

been given a different name (the **Dieckmann condensation**).^{134,135} This reaction involves intramolecular cyclization of an α, ω -diester such as **199**. The reaction is usually done under equilibrating conditions, although kinetic control conditions can also be used.



The initially formed enolate (200) attacked the ester group on the opposite side of the molecule to form a ring (tetrahedral intermediate 201). Loss of ethoxide in the usual manner gave β -keto-ester 202. Hydrolysis and thermally induced decarboxylation gave cyclopentanone.¹³⁴ A synthetic example is taken from Zhai and co-worker's synthesis of 19,20-dihydrosubincanadine B, in which diester 203 was treated with potassium *tert*-butoxide in THF and cyclization gave 204. Subsequent heating with acetic acid-HCl led to formation of the carboxylic acid *in situ*, and decarboxylation to give the ketone 205 in 81% overall yield.¹³⁶ There are many synthetic applications of the Dieckmann cyclization.



The Dieckmann disconnection is



The size of the ring being formed has a great influence on the course of the reaction. When **206** was treated with sodium ethoxide, three isomeric Dieckmann products were possible, **207-209**. Reaction of the enolate via path *a* may generate a three-membered ring, which is energetically

^{134. (}a) Dieckmann, W. Berichte, 1894, 27, 102, 965; (b) Idem, Ibid. 1900, 33, 2670; (c) Dieckmann, W.; Groenveld, A., Ibid. 1900, 33, 595; (d) Hauser, C.R.; Hudson, B.E. Org. React. 1942, 1, 266 (see p 274); (e) Schaefer, J.P.; Bloomfield, J.J. Ibid. 1967, 15, 1; (f) Reference 104, pp 124-125; (g) Reference 105, pp 75-77; (h) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-23; (i) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 204-205.

^{135.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd ed., Wiley-VCH, New York, 1999, pp 1316-1317.

^{136.} Liu, Y.; Luo, S.; Fu, X.; Fang, F.; Zhuang, Z.; Xiong, W.; Jia, X.; Zhai, H. Org. Lett. 2006, 8, 115.

less favorable. Attack of the enolate via path *b* would generate **209**, but this is disfavored due to the sterically hindered center adjacent to the enolate carbon. This leaves reaction paths *c* (to give **207**) and *d* (to generate **208**) as viable possibilities. What is the product? Reaction of **206** under these conditions gave **208** as the only product.¹³⁷ The yield of this product varied with the base used to initiate enolate formation.¹³⁷ The presence of the methyl group in **206** influences the course of the reaction and similar cyclization with the triester lacking that methyl gave a different major product.¹³⁷



9.4.B.iii. The Knoevenagel Condensation. Another classical reaction, called the Knoevenagel condensation^{138,133b} involves malonate enolates in a condensation reaction with aldehydes, usually a non-enolizable aldehyde. An aldehyde or ketone can be condensed with an active methylene compound (H_2CX_2 or $HRCX_2$) such as a malonic ester using a primary or secondary amine as the base. To avoid a competing aldol condensation, the aldehyde should have no α -protons. Diethyl malonate and benzaldehyde were condensed to form **210**, for example. Spontaneous elimination of water gave the alkylidene product (**211**), saponification followed by decarboxylation gave the final Knoevenagel product, conjugated acid **198**.

$$\begin{pmatrix} \text{CO}_2\text{Et} & \text{NHEt}_2 \\ \text{CO}_2\text{Et} & 2.\text{ H}_3\text{O}^+ \end{pmatrix} \begin{bmatrix} \text{Ph} & \text{CO}_2\text{Et} \\ \text{HO} & \text{CO}_2\text{Et} \end{bmatrix} \xrightarrow{-\text{H}_2\text{O}} \xrightarrow{\text{Ph}} & \text{CO}_2\text{Et} \\ \text{210} & \text{211} & 2.\text{ H}_3\text{O}^+ \\ \text{211} & 3.\text{ heat (-CO}_2) & 198 \end{pmatrix} \xrightarrow{\text{CO}_2\text{H}_2\text{O}} \xrightarrow{\text{CO}_2\text{H}_2$$

1 11 0110

Contrary to aldol condensation without conjugation in the products, elimination commonly occurs upon hydrolysis of the Knoevenagel products. This is a facile route to substituted methylene malonic acids $[RCH=C(CO_2H)_2]$ and acrylic acid derivatives. When the base is pyridine with a trace of piperidine (rather than diethylamine) and malonic acid is the enolate

^{137. (}a) Goldberg, M.W.; Hunziker, F.; Billeter, J.R.; Rosenberg, H.R. *Helv. Chim. Acta* 1947, 30, 200; (b) Banerjee, D.K. *J. Indian Chem. Soc.* 1940, 17, 453; (c) Chakravarty, N.K.; Banerjee, D.K. *Ibid.* 1946, 23, 377; (d) Dutta, J.; Biswas, R.N. *Ibid.* 1961, 38, 335.

⁽a) Japp, F.R.; Streatfeild, F.W. J. Chem. Soc. 1883, 43, 27; (b) Knoevenagel, F. Berichte 1896, 29, 172; (c) Idem, Ibid. 1898, 31, 730; (d) Jones, G. Org. React. 1967, 15, 204; (e) Reference 104, pp 261-262; (f) Reference 105, pp 148-149; (g) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-51; (h) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 364-365.



precursor, the reaction is called the **Doebner condensation** or the **Doebner modification**.¹³⁹ In a synthesis of (+)-hapalindole Q by Kerr and Kinsman,¹⁴⁰ malonic acid reacted

with aldehyde **212** in refluxing pyridine to give an 86% yield of **213**. Note that decarboxylation occurred under the reaction conditions. Kwon and co-workers showed that microwave irradiation facilitates the Knoevenagel condensation with aldehydes.¹⁴¹

Other derivatives containing two electron-withdrawing groups can be used in the reaction, including malononitrile (**215**). When condensed with 2,3-benzocycloheptanone (**214**), the dicyanoalkylidene product (**216**) was isolated in 46% yield.¹⁴² Cyanoacetic acid derivatives (such as ethyl 2-cyanoacetate) are also common partners in the Knoevenagel condensation.¹⁴³



As noted in Table 9.1, dinitromethane (217) has a p K_a of 3.6. Amines or even sodium carbonate are excellent bases for the deprotonation of 217 to give the resonance stabilized nitro-enolate 218. When this enolate anion reacted with piperonal, the dinitroalkylidene product 219 was formed in good yield. The **Henry reaction**¹⁴⁴ (also known as the **Kamlet reaction**) is closely related to this condensation, and is often called a **nitro aldol reaction**. The Henry reaction involves condensation of nitromethane (or another nitroalkane) with aldehydes or ketones. An example using nitro enolate $^{-}CH_2NO_2$ is the condensation of nitromethane with benzaldehyde to give a 75% yield of 1-nitro-2-phenylethene.¹⁴⁵ Mono-nitro compounds such as nitrobutane

- 142. Campaigne, E; Subramanya, R; Maulding, D.R. J. Org. Chem. 1963, 28, 623.
- 143. McElvain, S.M.; Lyle, Jr., R.E. J. Am. Chem. Soc. 1950, 72, 384.

144. (a) Henry, L. Compt. Rend. 1895, 120, 1265; (b) Kamlet, J. U.S. Patent 2,151,171, 1939 [Chem. Abstr. 33: 50039 1939]; (c) Hass, H.B.; Riley, E.F. Chem. Rev. 1943, 32, 373 (see p 406); (d) Lichtenthaler, F.W. Angew. Chem. Int. Ed. 1964, 3, 211. (e) For a review, see Luzzio, F.A. Tetrahedron 2001, 57, 915; (f) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-43; (g) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 300-301.

 ⁽a) Doebner, O. *Berichte, 1900, 33,* 2140; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-25; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions* and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 212-213.

^{140.} Kinsman, A.C.; Kerr, M.A. J. Am. Chem. Soc. 2003, 125, 14120.

 ^{141. (}a) Kim, S.-Y.; Kwon, P.-S.; Kwon, T.-W. Synth. Commun. 1997, 27, 533; (b) Kwon, P.-S.; Kim, Y.-M.; Kang, C.-J.; Kwon, T.-W. Synth. Commun. 1997, 27, 4091.

^{145.} Knoevenagel, E.; Walter, L. Berichte, 1904, 37, 4502.

can also react with a suitable base to generate an enolate anion, and then react with aldehydes or with ketones.¹⁴⁶ Several variations of this reaction include using microwave irradiation to assist the reaction¹⁴⁷ or Mg-Al hydrotalcites to induce condensation,¹⁴⁸ and using powdered KOH without solvent¹⁴⁹ or proazaphosphatranes [P(RNCH₂CH₂)₃N] to promote the reaction.¹⁵⁰ Asymmetric induction was observed in a synthesis of (–)-denopamine by Trost and co-workers¹⁵¹ when aldehyde **220** reacted with nitromethane, in the presence of diethylzinc and a chiral 2,6-diaminophenol derivative, to give nitro-aldol product **221** in 88% yield (90% ee).



Note that nitro enolates have other synthetic uses. When nitrobutane was treated with sodium hydroxide, nitro-enolate **222** was formed. Rather than addition of an aldehyde or a ketone, **222** was treated with concentrated sulfuric acid to form butanal with loss of N_2O , in what is known as the **Nef reaction**.¹⁵² Modern versions of this reaction use bases such as LDA and less vigorous oxidizing agents such as MoOPh.¹⁵³



The Knoevenagel disconnection is:

$$\begin{array}{|c|c|c|c|c|} \hline R & \hline CO_2H & \hline & R - CHO & + & HO_2C - CH_2 - CO_2H \\ \hline \end{array}$$

- 147. Varma, R.S.; Dahiya, R.; Kumar, S. Tetrahedron Lett. 1997, 38, 5131.
- 148. Bulbule, V.J.; Deshpande, V.H.; Velu, S.; Sudalai, A.; Sivasankar, S.; Sathe, V.T. Tetrahedron 1999, 55, 9325.
- 149. Ballini, R.; Bosica, G.; Parrini, M. Chem. Lett. 1999, 1105.
- 150. Kisanga, P.B.; Verkade, J.G. J. Org. Chem. 1999, 64, 4298.
- 151. Trost, B.M.; Yeh, V.S.C.; Ito, H.; Bremeyer, N. Org. Lett. 2002, 4, 2621.

153. Gabobardes, M.; Pinnick, H. Tetrahedron Lett. 1981, 22, 5235.

^{146.} Hass, H.B.; Susie, A.G.; Heider, R.L. J. Org. Chem. 1950, 15, 8.

⁽a) Nef, J.U. Annalen 1894, 280, 263; (b) Noland, W.E. Chem. Rev. 1955, 55, 137; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-64; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 452-453.

An interesting variation of the Knoevenagel condensation generates aldol condensation products (see Sec. 9.4.A). Condensation of β -keto esters and aldehydes at pH 7.8 in aqueous media gives the aldolate. The condensation of ethyl 3-oxobutanoate and pentanal gave 4-hydroxy-2-octanone in 80% yield.¹⁵⁴ This new methodology constitutes a regioselective alternative to the aldol condensation. Note that heating the β -hydroxy-ketone at pH 1 liberates a conjugated ketone, prepared from the keto-ester and aldehyde in a one-pot procedure.

9.4.B.iv. Nitrile Enolates. Nitrile enolates are formed by reaction of a nitrile with LDA or another suitable base. Nitrile enolates exist and react as aggregates,¹⁵⁵ with structures consistent with those found in the solid state.¹⁵⁶ Both alkylation¹⁵⁷ and condensation reactions with aldehydes¹⁵⁸ or ketones are known.¹⁵⁹ In addition to alkyl halides and carbonyl derivatives, condensation can occur with another nitrile. The base-catalyzed condensation of two nitriles to give a cyano-ketone via an intermediate cyano enolate, is known as the **Thorpe reaction**.^{160,134e} Reaction of butanenitrile with sodium ethoxide gave a nitrile enolate, which reacted with a second molecule of butanenitrile at the electrophilic cyano carbon to give **223**. Hydrolysis gave an intermediate imine-nitrile (**224**), which is in equilibrium with the enamine form (**225**, sec. 9.6.A). Hydrolysis led to the final product of the Thorpe reaction, an α -cyano ketone **226**.¹⁶⁰ Mixed condensations are possible when LDA and kinetic conditions are used to generate the α -lithionitrile (a mixed Thorpe reaction). When pentanenitrile was treated with LDA and condensed with benzonitrile, 2-cyano-1-phenyl-1-pentanone was the isolated product after acid hydrolysis. Nitrile enolates can also be alkylated with a variety of alkyl halides.¹⁶¹



^{154.} Kourouli, T.; Kefalas, P.; Ragoussis N.; Ragoussis V. J. Org. Chem. 2002, 67, 4615.

^{155.} Fleming, F.F.; Shook, B.C. J. Org. Chem. 2002, 67, 2885, and references 2b,c therein.

^{156.} Carlier, P.R.; Lo, K.M. J. Org. Chem. 1994, 59, 4053.

^{157.} For a synthetic example taken from a synthesis of (+)-neosymbioimine, see Varseev, G.N.; Maier, M.E. Org. Lett. 2007, 9, 1461.

^{158.} For a synthetic example taken from a synthesis of AM6898D, see Fukuda, Y.; Sakurai, M.; Okamoto, Y. *Tetrahedron Lett.* 2000, 41, 4173.

^{159.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd ed., Wiley-VCH, New York, **1999**, p 1317.

 ⁽a) Reference 104, p 449; (b) Baron H.; Remfry, F.G.P.; Thorpe, J.F. J. Chem. Soc. 1904, 85, 1726; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-93; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 646-647.

^{161.} Larchevêque, M.; Cuvigny, T. Tetrahedron Lett. 1975, 3851.

The Thorpe disconnection is:

	$R \longrightarrow R \longrightarrow X$
$R^1 \stackrel{\checkmark}{\sim} O$	$R^1 CN \longrightarrow R^1 X$

There is an intramolecular version of the Thorpe reaction called the **Thorpe-Ziegler reaction**.¹⁶² When an α, ω -dinitrile is treated with base, formation of the enolate is followed by cyclization. When adiponitrile (**227**) was treated with sodium ethoxide, cyclization gave the usual imineenamine mixture (**228**). Hydrolysis gave the cyano-ketone (2-cyanocyclopentanone, **229**).^{162b} In Deslongchamp's synthesis of (+)-martimol,⁷⁵ dinitrile **230** was treated with potassium *tert*butoxide in *tert*-butanol at 85°C, and after heating to 115°C with acetic acid-phosphoric acid ketone **231** was obtained in 68% yield.



The Thorpe-Ziegler disconnection is



9.4.B.v. The Stobbe Condensation. Condensation of succinic ester derivatives (such as diethyl succinate, 232) with non-enolizable ketones or aldehydes and a base gives the condensation product 233. The alkoxide reacts with the distal ester via acyl substitution to give a lactone intermediate (234). In the original version of this reaction, saponification of 234 gave the α -alkylidene monoester 235. The reaction is limited to those α, ω -diesters for which the Dieckmann condensation is not a competitive reaction so succinic acid derivatives are commonly used. This transformation is known as the Stobbe condensation.¹⁶³ The aldehyde or ketone substrate is not limited to non-enolizable derivatives. An example is the double-

^{162. (}a) Reference 104, pp 514-516; (b) Ziegler, K.; Eberle, H.; Ohlinger, H. Annalen 1933, 504, 94.

^{163. (}a) Stobbe, H. *Berichte* 1893, 26, 2312; (b) Stobbe, H. *Annalen* 1894, 282, 280; (c) Johnson, W.S.; Daub, G.H. *Org. React.* 1951, 6, 1; (d) Reference 104, pp 439-440; (e) Reference 105, pp 228-230; (f) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-90; (g) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 626-627.

Stobbe condensation of aldehyde **236** with diethyl succinate (sodium ethoxide was used as a base) to give **237**, taken from the Robinson and co-worker's synthesis¹⁶⁴ of dicaffeoyltartaric acid analogs.



The Stobbe disconnection is



9.4.B.vi. The Darzens' Glycidic Ester Condensation. When a α -halo ester is treated with base and the resulting enolate anion condensed with a carbonyl derivative, the product is a halo-alkoxide. This nucleophilic species can displace the halogen intramolecularly to produce an epoxide, which forms the basis of a classical reaction known as the Darzens' glycidic ester condensation.¹⁶⁵ Reaction of ethyl α -chloroacetate and sodium ethoxide in the presence of benzaldehyde generated the usual alkoxide (238). Intramolecular displacement of chloride, however, gave the glycidic ester (239). Saponification gave the epoxy acid (240), which was



unstable and lost carbon dioxide to generate a substituted aldehyde or ketone such as phenyl

^{164.} Reinke, R.A.; King, P.J.; Victoria, J.G.; McDougall, B.R.; Ma, G.; Mao, Y.; Reinecke, M.G.; Robinson, Jr., W.E. J. Med. Chem. 2002, 45, 3669.

^{165. (}a) Darzens, G. Compt. Rend. 1904, 139, 1214; (b) Idem Ibid. 1906, 142, 214; (c) Ballester, M. Chem. Rev. 1955, 55, 283; (d) Reference 104, pp 116-118; (e) Reference 105, pp 68-70; (f) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-22; (g) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 198-199.

acetaldehyde in this case. This sequence is a useful **chain extension reaction** in which an aldehyde (PhCHO) is converted to a longer chain aldehyde homolog (PhCH₂CHO). A ketone is converted to a longer chain aldehyde. An enantioselective synthesis of glycidic amides using camphor-derived sulfonium salts has been reported.¹⁶⁶ Cyclohexanone, for example, reacted with ethyl α -chloroacetate in the presence of *tert*-butoxide to give cyclohexane carboxaldehyde via hydrolysis of the initially formed glycidic ester.¹⁶⁷ Using a α -alkyl- α -chloroester in this sequence leads to a ketone as the final product. An asymmetric version of this reaction isknown,

in which (–)-8-phenylmenthyl ester of chloroacetic acid (**241**) reacted with acetone to give a 64% yield of **242**, in 87% de.¹⁶⁸ A catalytic asymmetric Darzens condensation¹⁶⁹ has been reported



using a chiral phase transfer agent. Note that a Wittig reaction that produces a vinyl ether (Ph₃P=CHOR + ketone \rightarrow R₂C=CHOR) that can be hydrolyzed to a chain extended aldehyde (sec. 8.8.A.i). It is an attractive alternative to the Darzens' glycidic ester condensation.

The Darzens' disconnection is

$$\begin{array}{c} Ar \\ (R^1) \\ O \\ O \\ O \\ O \\ CO_2H \end{array}$$

9.4.B.vii. Acid Dianions. All of the named reactions discussed in Section 9.4 constitute relatively minor variations of the fundamental condensation reaction of aldehydes, ketones or acid derivatives with another aldehyde, ketone, or acid derivative. The ability to produce kinetic enolates from acid derivatives has made possible another useful modification of the enolate reaction. Carboxylic acids have an acidic proton that is removed by one equivalent of base to first give a carboxylate (see 243). Addition of a second equivalent of a powerful base such as a dialkylamide leads to the dianion (244). Subsequent reaction with an electrophilic

$$H_{3}C-CO_{2}H \xrightarrow{LDA} [H_{3}C-CO_{2}^{-}] \xrightarrow{LDA, THF} [H_{2}C-CO_{2}^{-}] \xrightarrow{1. n-C_{4}H_{9}Br} n-C_{4}H_{9}-HC-CO_{2}H$$

species, in this case 1-bromobutane, occurred first at the more nucleophilic α -carbon to give hexanoic acid.¹⁷⁰ The carboxylate is usually generated with *n*-butyllithium and the enolate with LDA, although two equivalents of LDA can be used. As discussed in Chapter 8, treatment

^{166.} Aggarwal, V.K.; Charmant, J.P.H.; Fuentes, D.; Harvey, J.N.; Hynd, G.; Ohara, D.; Picoul, W.; Robiette, R.; Smith, C.; Vasse, J.-L.; Winn, C.L. J. Am. Chem. Soc. 2006, 128, 2105.

^{167.} Hunt, R.H.; Chinn, L.J.; Johnson, W.S. Org. Synth., Coll. Vol. 4 1963, 459.

^{168.} Ohkata, K.; Kimura, J.; Shinohara, Y.; Takagi, R.; Hiraga, Y. Chem. Commun. 1996, 2411.

^{169.} Arai, S.; Shioiri, T. Tetrahedron Lett. 1998, 39, 2145.

^{170. (}a) Reference 2b, p 158; (b) Pfeffer, P.E.; Silbert, L.S.; Chirinko, Jr., J.M. J. Org. Chem. 1972, 37, 451.

of a carboxylic acid with an organolithium reagent usually gives the ketone, via reaction of the carboxylate (243) with a second equivalent of an organolithium reagent (sec. 8.5.E).¹⁷¹ For this reason, dialkylamides are commonly employed for the second deprotonation.¹⁷² An acid dianion gives the typical reactions of enolates derived from acid derivatives.¹⁷³ When 3-methylbutanoic acid was treated first with sodium hydride and then with LDA, dianion 245 was formed.¹⁷⁴ The more acidic carboxylic acid proton was removed by the first equivalent of base, and least acidic hydrogen (the α -hydrogen) was removed with the send equivalent of base, and that position is the more nucleophilic center in 245. Therefore, subsequent reaction with 4-bromo-1-butene occurred exclusively at the α -position, and hydrolysis gave an 95% yield of 246, as reported in Koskinen and co-worker's synthesis of nor-1,6-germacradien-5-ols.¹⁷⁴



Dianions of this type react with ketones,¹⁷⁵ epoxides¹⁷⁶ or esters¹⁷⁷ as well as a wide variety of other electrophiles. The dilithio derivative of 2-methylpropionic acid was condensed with the epoxide moiety in **247** to form an hydroxy acid, which cyclized to form the lactone ring in **248**.¹⁷⁶ Since most of the enolates of acid derivatives contain a leaving group, the alkoxide resulting from reaction with an epoxide often displaces that leaving group to give the lactone.



The condensation of enolates with alkyl halides or other carbonyl derivatives allows a wide variety of synthetic and functional group transformations in the carbon-carbon bond-forming process. Enolates are, therefore, among the most powerful synthetic intermediates known. In addition to generating a new carbon-carbon bond, the reaction proceeds with high diastereoselectivity in most cases, making it even more useful.

- 171. Heathcock, C.H.; Gulik, L.G.; Dehlinger, T. J. Heterocyclic Chem. 1969, 6, 141.
- 172. For a convenient preparation, see Parra, M.; Sotora, E.; Gil, S. Eur. J. Org. Chem. 2003, 1386.
- 173. Petragnani, N.; Yonashiro, M. Synthesis 1982, 521.
- 174. Nevalainen, M.; Koskinen, A.M.P. J. Org. Chem, 2002, 67, 1554.
- 175. Moersch, G.W.; Burkett, A.R. J. Org. Chem. 1971, 36, 1149.
- 176. (a) Creger, P.L. J. Org. Chem. 1972, 37, 1907; (b) Creger, P.L. J. Am. Chem. Soc. 1967, 89, 2500.
- (a) Kuo, Y.N.; Yahner, J.A.; Ainsworth, C. J. Am. Chem. Soc. 1971, 93, 6321; (b) Pfeffer, P.F.; Silbert, L.S. Tetrahedron Lett. 1970, 699.
9.4.C. The Mukaiyama Aldol Reaction

The acid-catalyzed aldol condensation was mentioned briefly in Section 9.4.A.i, including a reaction catalyzed by TiCl₄. Using traditional Brønsted-Lowry acids generates the aldolate product, but the acidic conditions make the process reversible and poor yields can result as well as deleterious cationic side reactions. For these reasons, this variation is not as widely used as the anionic reaction (the aldol condensation). The base catalyzed reaction often leads to dimers, polymers, self-condensation products or α,β -unsaturated carbonyl derivatives, as described in Section 9.4.A. Mukaiyama and co-workers modified the acid-catalyzed reaction to include silvl enol ethers. They found a reacton with carbonyl compounds produced aldollike products, in the presence of titanium tetrachloride (TiCl₄) and other Lewis acids (e.g. BF₃•OEt₂, TMS-OTf).¹⁷⁸ The requisite silvl-enol ether is prepared by treatment of a ketone such as diphenylacetone (249) with base and trapping the thermodynamic enolate with chlorotrimethylsilane, to give 250. The concept of trapping enolates with chlorotrimethylsilane was briefly introduced in Section 9.3.B. When 250 was mixed with an aldehyde such as 3-phenylpropanal, in the presence of TiCl₄, a condensation occurred via a transition state such as 251 to produced the titanium aldolate 252 via loss of chlorotrimethylsilane. Hydrolysis provided the aldol product 253. The reaction proceed without self-condensation and at -78° C. This reaction is now called the Mukaiyama aldol reaction.¹⁷⁹ Other Lewis acids can initiate this coupling, including tin tetrachloride ($SnCl_4$) and boron trifluoride etherate ($BF_3 \cdot OEt_2$).



Mukaiyama et al.¹⁸⁰ showed that the reaction of **254** with benzaldehyde and various Lewis acids generated the aldolate (**255**), the trimethylsilyl alkoxide (**256**) and the alkylidene elimination product (**257**). These results are shown in Table 9.7,¹⁸⁰ and it is clear that titanium tetrachloride

^{178.} Inomata, K.; Muraki, M.; Mukaiyama, T. Bull. Chem. Soc. Jpn. 1973, 46, 1807.

⁽a) Mukaiyama, T. Angew. Chem. Int. Ed. 1977, 16, 817; (b) Mukaiyama, T. Org. React. 1982, 28, 203 (see pp 238-248); (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-63; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 440-441.

^{180.} Mukaiyama, T.; Banno, K.; Narasaka, K. J. Am. Chem. Soc. 1974, 96, 7503.

(TiCl₄) and tin tetrachloride (SnCl₄) are the best catalysts, although boron trifluoride (BF₃•OEt₂) and zinc chloride (ZnCl₂) also gave good results. In a reaction taken from Taylor and Jin's synthesis of the C8-C19 region of peloruside A,¹⁸¹ the silyl enol ether reacted with aldehyde **258** in the presence of boron trifluoride ether54321ate, to give the aldol product **259** in 91% yield as an 8:1 mixture. Silyl-enol ethers generally show good selectivity for reaction with aldehydes, even in the presence of a ketone moiety.^{175,182} Condensation does occur with ketones, however, if no aldehyde carbonyl is available and ketones react faster than esters.¹⁸³ Denmark and Stavenger showed that trichlorosilyl enolates are very competent aldol reagents, even in the absence of additives.¹⁸⁴

 Table 9.7.
 Reaction of Silyl Enol Ethers with Benzaldehyde in the Presence of Lewis Acids

$\begin{array}{ c c c } OSiMe_3 & 1. \\ \hline \\ \hline \\ 254 \end{array}$	PhCHO, MX_n CH_2Cl_2 H_2O	0 OH ↓ Ph + 255	0 OSiM 0 OSiM 4 256	he_3 +	257		
Lewis Acid	Temp. (°C)	Time (h)	% 255	% 256	% 257		
TiCl ₄	RT	2	82	trace	2		
TiCl ₄	-78	1	92	0	0		
SnCl ₄	RT	1	33	trace	28		
SnCl ₄	-78	1	83	trace	trace		
FeCl ₃	RT	1	0	0	12		
AlCl ₃	RT	1	55	trace	trace		
BCl ₃	RT	1	26	0	0		
BF ₃ •OEt ₂	-78	1	80	12	0		
ZnCl ₂	RT	10	69	8	3		
SnCl ₂	-78	12	trace	0	0		
Bu ₃ SnCl	RT	24	0	0	0		
MgCl ₂	RT	24	0	0	0		
CdCl ₂	RT	24	0	0	0		
LiCl	RT	24	0	0	0		
[Reprinted with permission from Mukaiyama, T.; Banno, K.; Narasaka, K. J. Am. Chem. Soc. 1974, 96, 7503. Copyright © 1974 American Chemical Society.]							
OTIPS OTBS C	ОМе СНО В	$\overbrace{F_3 \bullet OEt_2, CH_2C}^{OSiMe_3}$		OTIPS OTBS (OMe OH C		

Diastereoselectivity was initially poor in the Mukaiyama reaction, often giving a mixture of syn-and anti- diastereomers in approximately a 1:1 ratio. When complexing agents are added

184. Denmark, S.E.; Stavenger, R.A. J. Am. Chem. Soc. 2000, 122, 8837.

^{181.} Taylor, R.E.; Jin, M. Org. Lett. 2003, 5, 4959.

^{182.} See Mukaiyama, T.; Narasaka, K.; Banno, K. Chem. Lett. 1973, 1011.

^{183.} Bohlmann, F.; Eickeler, E. Chem. Ber. 1979, 112, 2811.

to the reaction medium, good diastereoselectivity can be obtained (sec. 9.5.A.v, see below), and some asymmetric induction is possible when chiral catalysts are used. Stereochemically pure aldehydes such as **258** lead to good diastereoselectivity. The reaction of benzaldehyde with **260** gave a 74% yield of **262** (3.2:1 syn/anti),¹⁸⁵ in the presence of cupric triflate and bis(oxazolidine) catalyst **261**. Interestingly, this reaction was done in aqueous media. A water-accelerated reaction of ketene silyl acetals has been reported.¹⁸⁶



The bis(oxazolidine) catalyst can be applied to silyl enol ethers as well, and good asymmetric induction can be achieved. (*R*)-BINOL-Titanium catalysts have been used in solvents such as toluene or CH_2Cl_2 ,¹⁸⁷ and also in supercritical fluoroform and in supercritical carbon dioxide. Other reactions have been reported using catalysts closely related to **261** and dichloromethane as the solvent.¹⁸⁸ Chiral oxazaborolidinone derivatives are effective catalysts for enantioselective Mukaiyama aldol reactions.¹⁸⁹ In a synthesis of halipeptins A and D by Nicolaou and coworkers,¹⁹⁰ aldehyde **263** was condensed with Me₂C=C(OMe)OTMS in the presence of **264** to give **265** in 87% yield and about 95:5 diastereoselectivity.



A variation of the Mukaiyama aldol reaction involves the reaction of silyl enol ethers with acetals,¹⁹¹ in the presence of TiCl₄. An example is the reaction of silyl-enol ether **266** with 1,1-dimethoxycyclohexane (**267**, a protected cyclohexanone, sec. 7.3.B.i) to give **268** in 91% yield.^{192,193,194}

- 189. Ishihara, K.; Kondo, S.; Yamamoto, H. J. Org. Chem. 2000, 65, 9125.
- Nicolaou, K.C.; Lizos, D.E.; Kim, D.W.; Schlawe, D.; de Noronha, R.G.; Longbottom, D.A.; Rodriquez, M.; Bucci, M.; Cirino, G.J. Am. Chem. Soc. 2006, 128, 4460.
- 191. Mukaiyama, T.; Murakami, M. Synthesis 1987, 1043.
- 192. Mukaiyama, T.; Hayashi, M. Chem. Lett. 1974, 15.
- 193. Ishihara, H.; Inomata, K.; Mukaiyama, T. Chem. Lett. 1975, 531.
- 194. Mukaiyama, T.; Ishihara, H.; Inomata, K. Chem. Lett. 1975, 527.

^{185. (}a) Kobayashi, S.; Nagayama, S.; Busujima, T. Chem. Lett. 1999, 71; (b) Idem Tetrahedron 1999, 55, 8739.

^{186.} Loh, T.-P.; Feng, L.-C.; Wei, L.-L. Tetrahedron 2000, 56, 7309.

^{187.} Mikami, K.; Matsukawa, S.; Kayaki, Y.; Ikariya, T. Tetrahedron Lett. 2000, 41, 1931.

^{188.} Evans, D.A.; Burgey, C.S.; Kozlowski, M.C.; Tregay, S.W. J. Am. Chem. Soc. 1999, 121, 686.



Mukaiyama conditions were used intramolecularly for the successful closure of an 11-membered ring in Smith and co-worker's synthesis of normethyljatrophone.¹⁹⁵ Conversion of the alkynyl conjugated yn-one moiety in **269** to a silyl-enol ether, was followed by reaction with TiCl₄ and reaction with the dioxolane moiety. Ring closure (sec. 7.3.B.i for formation of dioxolanes) gave **270** in 47% yield.¹⁹⁵



Conjugated ketones react with silyl-enol ethers under Mukaiyama conditions to give the 1,4-addition product in high yield. Reaction of **254** with **271**, for example, gave a 95% yield of the 1,4-product (**272**).¹⁹⁶ Aldol condensations with conjugated systems often lead to 1,4-addition of the enolate anion (sec. 9.7.A). Since the aldol condensation is usually done under basic conditions, further reaction of the products including self-condensation of the starting materials is commonly observed. Mukaiyama conditions are relatively mild, and the 1,4-addition proceeds in good yield with few deleterious side reactions.



The Mukaiyama reaction can also be applied to ketene acetals such as **274**, derived from the enolate anion of an ester such as that in **273**. In a synthesis of a novel angiogenesis inhibitor (–)-azaspirene by Hayashi and co-workers,¹⁹⁷ **273** reacted with LDA to give the enolate anion and reaction with with *tert*-butyldimethylsilyl triflate gave **274**. Subsequent condensation with phenylpropargyl aldehyde, mediated by magnesium bromide, gave **275** in 69% yield (about 92% de). Other Lewis acids were used in this reaction, but they gave **275** with much poorer

^{195.} Smith III, A.B.; Guaciaro, M.A.; Schow, S.R.; Wovkulich, P.M.; Toder, B.H.; Hall, T.W. J. Am. Chem. Soc. 1981, 103, 219.

^{196. (}a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223; (b) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779.

^{197.} Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 12078.

diastereoselectivity. This variation is very useful since esters can be used as ketene acetal precursors, greatly expanding the utility of the reaction.



The disconnections are identical to those shown for the aldol condensation.

9.4.D. Boron Enolates

Vinyl boronates (boronic esters such as **276**) are important intermediates in directed aldol condensations, particularly when derived from aldehydes. Trapping the enolate as the boronic ester, and separating the desired isomer, can solve regiochemical problems in enolate formation. Subsequent condensation proceeds with excellent diastereoselectivity (sec. 9.5). Mukaiyama and co-workers showed that conjugate addition of tri-*n*-propylborane (sec. 5.2.A) with methyl vinyl ketone gave **276**, and reaction with benzaldehyde gave a 91% yield of **277:278** as a 33:1 mixture of diastereomers.^{198,199,178} Mukaiyama's conjugate addition method for the preparation of **276** was first reported by Brown.²⁰⁰ Masamune also prepared **276** via reaction of diazoketone **279** with tributylborane (sec. 13.9.C for the preparation and other reactions of diazoketones).¹⁹⁸ Other methods for the preparation of boron enolates include the reaction of borane derivatives with ketones, thioesters or ketone enolates (see below).



There are several interesting features of the boron enolate aldol condensation. The condensation reaction that produced **277** and **278** clearly proceeded with good diastereoselectivity, and is analogous to that observed in base-catalyzed enolate condensations (sec. 9.5). It is important to note that the boron aldolate product was treated with an oxidizing agent to remove boron (just as boranes were oxidized in Chap. 5). The two most common oxidants are H_2O_2 and MoOPh,²⁰³ which did not degrade the diastereoselectivity of the initial condensation. Several factors help to control or at least influence the diastereoselectivity of the reaction. The first is the geometry

^{198.} Masamune, S.; Mori, S.; Van Horn, D.; Brooks, D.W. Tetrahedron Lett. 1979, 1665.

^{199.} Mukaiyama, T.; Inomata, K.; Muraki, M. J. Am. Chem. Soc. 1973, 95, 967.

^{200.} Suzuki, A.; Arase, A.; Matsumoto, H.; Itoh, M.; Brown, H.C.; Rogić, M.M.; Rathke, M.W. J. Am. Chem. Soc. 1967, 89, 5708.

of the boron enolate. In most preparations, the (E)-isomer of boron enolate 276 predominates. This isomer led to 277 with high diastereoselectivity. Masamune found that treatment of 276 with lithium phenoxide led to isomerization of the (E)-isomer to the (Z)-isomer,¹⁹⁸ and subsequent condensation with benzaldehvde gave a 90% vield of 277 and 278 (>2:1 ratio). Masamune also found that the geometry of the boron enolate was greatly influenced by its method of preparation. Tributylborane reacted with methyl vinyl ketone (MVK) to give predominantly the (E)-isomer, as shown. Ketene 280 reacted with sulfide Bu_2BSt -Bu to give the (E)-enolate (281) as the major isomer. Condensation with isobutyraldehyde gave a 75% yield of 282 and 283, in a ratio of 5:>95 favoring 283.²⁰¹ Masamune also showed that boron enolates are generated by reaction of a thioester (284) with dibutylboryl triflate and diisopropylethylamine (Hünigs base). The product of this reaction was boron enolate 285, and subsequent condensation with isobutyraldehyde gave 282 and 283, although the diastereomeric ratio was reversed to give a >95:5 ratio (79% yield) favoring 282.¹⁹⁶ A similar reaction occurs with enolizable ketones such as 286, where the syn:anti ratio of the aldolate products resulting from reaction of the boron enolate (287) varied as Hünigs base or 2,6-lutidine was used as the base.²⁰² The best selectivity for the syn-diastereomer (287) was observed with 9-BBN derivatives, and the best anti-diastereoselectivity (288 > 289) was with dicyclopentylboranes and Hünigs base.



The diastereoselectivity of the aldol condensation varies with the substituents on the carbonyl precursor to the boron enolate. The boron enolates derived from ketones such as **290** are shown in Table 9.8.²⁰³ The lithium enolate of **290** reacted with a boron triflate to give the (Z) enolate **291** and the (E) enolate **292**. Reaction with an aldehyde such as benzaldehyde gave the syn (**293**) and the anti boron aldolate (**294**). The boron aldolates were converted to the

^{201.} Hirama, M.; Masamune, S. Tetrahedron Lett. 1979, 2225.

^{202.} Van Horn, D.E.; Masamune, S. Tetrahedron Lett. 1979, 2229.

^{203.} Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. J. Am. Chem. Soc. 1981, 103, 3099.

aldolate by treatment with H_2O_2 or MoOPH.²⁰³ The results were similar to those observed by Masamune. The best selectivity was obtained in an ether solvent with the enolate and product ratios a function of the base. Hünigs base gave a (*Z*/*E*) ratio of >99:1 whereas lutidine gave a 69:31 ratio. The ligand (L) was important and L = *n*-Bu led to a (*Z*/*E*) ratio of 99:1, whereas L = cyclopentyl gave 84:16.^{203,204}

$\frac{1}{R^1} \frac{1}{2} \frac{1}{2}$	L. base 2. L₂BOTf Hünigs base	$R^{1} \xrightarrow{OBL_{2}} Me^{+}$ 291	$R^{1} \xrightarrow{Me} Me \xrightarrow{PhCHO} PhCHO$	$R^{1} \underbrace{\overset{O OBL_{2}}{\underset{Me}{\overset{Me}{}}}_{R} + 293}$	$R^{1} \underbrace{\overset{O OBL_{2}}{\overset{I}{\underset{Me}{\underline{Me}}}}}_{R} R^{1} \underbrace{\overset{I}{\underset{Me}{\underline{Me}}}}_{R} R^{1} \underbrace{\overset{I}$	
	<u>R</u> 1	<u> 291 : 292</u>	<u> 293 : 294</u>	% Yield		
	Et	>99:1	>97:3	77		
	Ph	>99:1	>97:3	82		
	<i>i</i> -Bu	>99:1	>97:3	82		
	<i>i</i> -Pr	45 : 55	44 : 56	92		
	<i>i</i> -Bu	>99:1	>97:3	65		
[Reprinted with permission from Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. J. Am. Chem. Soc. 1981, 103, 3099 and Evans, D.A.; Bartroli, J.; Shih, T.L. J. Am. Chem. Soc. 1981, 103, 2127. Copyright © 1981 American Chemical Society.]						

 Table 9.8.
 Selectivity in Boron Enolate Aldol Condensations

Modern versions of this condensation react dialkylchloroboranes with ketones or aldehydes, in the presence of an amine base. A synthetic example of this reaction is taken from Paterson and co-worker's studies toward the synthesis of spirastrellolide A^{205} Ketone **295** was treated with the chiral B-chloro diisopinocampheylborane (see Chap. 5) in the presence of triethylamine to give the boron enolate *in situ*, which reacted with aldehyde **296** to give an 87% % yield of **297** with a diastereoselectivity of >20:1.



9.4.E. The Meyers Aldehyde Synthesis

Groups other than a carbonyl can stabilize a carbanion. Meyers and co-workers²⁰⁶ described the preparation of α -lithio derivatives of dihydro-1,3-oxazines (**298**) and 2-oxazolines (**300**), and subsequent alkylation and condensation



^{204.} Evans, D.A.; Bartroli, J.; Shih, T.L. J. Am. Chem. Soc. 1981, 103, 2127.

^{205.} Paterson, I.; Anderson, E.A.; Dalby, S.M.; Loiseleur, O. Org. Lett. 2005, 7, 4125.

^{206.} Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R. J. Am. Chem. Soc. 1969, 91, 763.

reactions via α -lithio derivatives such as (299). Meyers and co-workers treated the commercially available **301** with *n*-butyllithium to form the α -lithio derivative (**302**), stabilized by chelation with the nitrogen. When iodomethane was added, a carbanion displacement reaction occurred to give **303**.²⁰⁶ Reduction of the imine unit in **303** with borohydride (sec. 4.4.A) gave amine **304**, and hydrolysis produced the aldehyde (propanal). When **302** was treated with benzophenone, the initial condensation product after hydrolysis was the alcohol (**305**). Reduction of the imine moiety provided **306**²⁰⁷ and hydrolysis led to conversion of the oxazolidine to aldehyde **307**, but this eliminated water under the hydrolysis conditions to give the conjugated aldehyde (**308**). This sequence is known as the **Meyers' aldehyde synthesis**.^{206,208} Table 9.9^{206,207} shows formation of both the alkylation product and the condensation product derived from the nucleophile **302**. The reaction of lithio derivative **302** with alkyl halides leads to aldehydes such as **309**, and reaction with aldehydes or ketones leads to conjugated carbonyl derivatives such as **310**.



Table 9.9.Aldehyde Formation via Alkylation and Condensation with Dihydro-1,3-
Oxazine (301)

$Me \xrightarrow{Me}_{N} Me \xrightarrow{Me}_{CH}$	<u><i>n</i>-C₄H</u>	9Li → Me− Me	Me $\downarrow 0$ $\downarrow 1$ Li 302	$\begin{array}{c} 1. \text{ R}-X\\ 2. \text{ NaBH}_4\\ \hline 3.\text{H}_3\text{O}^+\\ \hline 0\\ 1. \\ R^2\\ \hline R\\ \hline 2. \text{ H}_2\text{O}\\ 3. \text{ NaBH}_4; \end{array}$	$\begin{array}{c} \bullet \\ H \\ \hline 309 \\ \hline \\ H_{3}O^{+} \end{array} =$	R R ² H 310
<u>R</u>	X	<u>% 309</u> ª		<u>R</u> 1	<u>R²</u>	<u>% 310ª</u>
Me	Ι	60		C_3H_7	Н	61
<i>n</i> -Pr	Ι	65		C ₆ H ₁₃	Н	48
<i>n</i> -Bu	Br	67		Ph	Н	64
CH ₂ =CHCH ₂	Br	53		Me	Me	50
<i>i</i> -Pr	Ι	47		-(CH ₂)5-	53
PhCH ₂	Br	54		Et	Et	62
				Ph	Me	50
^a overall yield from	n 301			Ph	Ph	62
[Reprinted with permission from Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R. J. Am. Chem. Soc. 1969 , 91, 763 and Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Fitzpatrick, J.M.; Malone, G.R.; Politzer, I.R. J. Am. Chem. Soc. 1969 , 91, 764. Copyright © 1969 American Chemical Society.]						

^{207.} Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Fitzpatrick, J.M.; Malone, G.R.; Politzer, I.R. J. Am. Chem. Soc. 1969, 91, 764.

^{208. (}a) Meyers, A.I.; Nabeya, A.; Adickes, H.W.; Politzer, I.R.; Malone, G.R.; Kovelesky, A.C.; Nolen, R.L.; Portnoy, R.C. J. Org. Chem. 1973, 38, 36; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-61.



Meyers and others²⁰⁹ showed that 2-oxazolines such as **311** are carbanionic synthons when they are converted to their α -lithio derivative. Reaction of **311** with *n*-butyllithium, for example, gave **312**. Addition of benzyl bromide gave the alkylated product **313**, and heating that product in ethanolic sulfuric acid gave an 84% yield of the ethyl ester, ethyl 3-phenylpropanoate (**314**).²¹⁰ Ketones react similarly to give a conjugated acid derivative.

$$\begin{array}{c} & & & \\ & & & & \\ & & & \\ & & & & \\ & & & \\ & & & &$$

These reactions are not limited to the simple oxazine and oxazolines described above. They are readily prepared from aldehydes and amino alcohols. Meyers used this methodology to prepare chiral precursors for use in asymmetric synthesis. When keto-acid **315** was treated with valinol (**316**), chiral bicyclic lactam **317** was formed.²¹¹ Sequential alkylations with iodomethane and then 4-methoxybenzyl bromide gave **318** in 85% yield (30:1 selectivity). Upon hydrolysis, keto acid **319** was produced in 88% yield with > 98% ee.¹⁷⁹ Alkylation of **317**, or related analogs, proceeds with excellent diastereoselectivity, as seen in Meyers and co-worker's asymmetric synthesis of (+)-mesembrine.²¹²



It is clear that the Meyers aldehyde synthesis provides a facile route not only to a variety of aldehydes but also to esters, acids, and chiral derivatives. The disconnections available by this methodology include

^{209.} For related work, see (a) Wehrmeister, H.L. J. Org. Chem. 1962, 27, 4418; (b) Allen, P.; Ginos, J. Ibid. 1963, 28, 2759.

^{210.} Meyers, A.I.; Temple, Jr., D.L. J. Am. Chem. Soc. 1970, 92, 6644, 6646.

^{211.} Meyers, A.I.; Harre, M.; Garland, R. J. Am. Chem. Soc. 1984, 106, 1146.

^{212.} Meyers, A.I.; Hanreich, R.; Wanner, K. Th. J. Am. Chem. Soc. 1985, 107, 7776.

$$\begin{array}{c} OHC & R & \swarrow HO_2C-Me + R-X \\ OHC & & (X = CO_2H \text{ or }CHO); \\ R & & (X = CO_2H \text{ or }CHO); \\ X & & (X = CO_2H + R^1 - X + R^2 - X) \end{array} \qquad \begin{array}{c} EtO_2C & R^1 \\ EtO_2C & R^1 \\ OHC & R^1 \\ OHC & R^1 \end{array} \qquad \begin{array}{c} HO_2C-Me + O \\ R^1 & R^1 \\ OHC & R^1 \end{array}$$

MOLECULAR MODELING: Where Steric Considerations May Not Be Sufficient

In some cases steric effects revealed by 2D drawings or even accurate 3D models may not lead to a clear assignment of product, or even to a prediction of the wrong product. Either steric effects are not the controlling factor, or, if they are, they may not be easy to anticipate from a structural model. An example is provided by reaction of 4-methoxybenzyl bromide with the enolate anion formed from **A**. The major product, **318**, follows from reaction of the enolate anion (**B**) with the electrophilic carbon of the benzylic bromide on the "concave" face of the bicyclic enolate.



Examine a space-filling model of **B**. Is the convex face (lower left) visually more crowded than the concave face (upper left)? Are you able to predict the observed product?

Next examine the local ionization potential map for **B** (right). This shows whether electrons are tightly bound ("blue") or loosely bound ("red") as a function of location on the accessible surface of the enolate. The more loosely bound the electrons the more likely they will be donated to an electrophile. Is the convex or concave face of the enolate more susceptible to attack by an electrophile? Does the more reactive face lead to the observed product?

9.4.F. Imine and Hydrazone Carbanions

In Section 9.4.A, it was noted that there were problems with aldol-type reactions, especially with the directed aldol condensation. In particular, aldehydes with an α -hydrogen have great difficulty adding to ketones due to their propensity for self-condensation. The ability to use kinetic control conditions in enolate reactions of ketones and aldehydes often solves this problem. There are also several alternative approaches that involve the use of carbanions derived from imines and hydrazones and these can be very useful.²¹³

9.4.F.i. Imine Carbanions. Wittig prepared the ethylamine imine of acetaldehyde (see **320**), and subsequent reaction with lithium diethylamide gave α -lithio derivative **321**. When benzophenone was added, the expected carbanion condensation reaction occurred to give a

^{213.} Wittig, G.; Reiff, H. Angew. Chem. Int. Ed. 1968, 7, 7.

27% yield of **322**.^{214,215} With these experiments, Wittig and co-workers demonstrated several important features of imine carbanions. The imine moiety functioned as a protected carbonyl (see sec. 7.3.B for protecting groups used with ketones and aldehydes) in this reaction, and the carbonyl could be regenerated after the alkylation or condensation reaction. The imine clearly provides activation to the α -position to produce the carbanion on treatment with a suitably strong base. For Schiff bases (imines derived from aldehydes) deprotonation can occur only at the α -carbon, with no possibility of self-condensation or dimerization. The sequence shown above was one of the first examples of an aldehyde directed aldol condensation.



In a synthesis of the phomoidrides by Nicolaou and co-workers,²¹⁶ imine **323** was treated with LDA, and then the aldehyde to generate a substituted imine. Subsequent acid hydrolysis converted the imine to an aldehyde, with accompanying elimination of water to give a 50% overall yield of conjugated aldehyde **324**. When imine anions of this type are condensed with an ester, the product is an enamino ketone.²¹⁷ There is a potential problem when this approach is used. When imine carbanions react with ethyl chloroformate, two products are usually formed; *C*-acylation as the major product and *N*-acylation as a minor product.²¹⁸



The imine-carbanion method was modified to accomplish the interesting ketone \rightarrow conjugated aldehyde transformation. The α -lithioimine (**325**) reacted with cyclohexanone to give **326**. Hydrolysis at a carefully controlled pH of 4.5 led to a conjugated aldehyde **327** in 90% yield.²¹⁹



- 214. Wittig, G.; Frommeld, H.-D. Chem. Ber. 1964, 97, 3541.
- 215. Wittig, G.; Frommeld, H.-D. Chem. Ber. 1964, 97, 3548.
- 216. Nicolaou, K.C.; Jung, J.; Yoon, W.H.; Fong, K.C.; Choi, H.-S.; He, Y.; Zhong, Y.-L.; Baran, P.S. J. Am. *Chem. Soc.* **2002**, *124*, 2183.
- 217. Wittig, G.; Suchanek, P. Tetrahedron Suppl. 8, Part I 1966, 22, 347.
- 218. Reference 213, p 12 and citation 6 therein.
- 219. Corey, E.J.; Enders, D.; Bock, M.G. Tetrahedron Lett. 1976, 7.

9.4.F.ii. Hydrazone Carbanions. Corey and Enders²²⁰ introduced an alternative to Wittig's imine-carbanion methodology discussed in Section 9.4.F.i. Modification of the reaction to use a hydrazone rather than an imine made it more controllable and useful. In a synthesis of (+)-leucascandroide A by Paterson and Tudge,²²¹ hydrazone **328** (PMB = *p*-methoxybenzl) was converted to the anion with LDA and subsequent reaction with the propargylic bromide gave **329**. Subsequent treatment with tetrabutylammonium fluoride (TBAF) initiated conversion of the hydrazone to the ketone and the *O*-silyl group to the alcohol (sec. 7.3.A.i), giving **330** in 65% yield. The hydrazone carbanion reacts like other carbanions, not only with alkyl halides but with other electrophilic species such as carbonyl derivatives or epoxides.²²² This is illustrated by the reaction of the *N*,*N*-dimethylhydrazone derivative of cyclohexanone (**331**) with LDA and then with benzophenone, to give a 90% yield of **332**.²²³ Hydrazone carbanions generally show a great preference for 1,2-addition to conjugated aldehydes such as crotonaldehyde,²²³ which suggests that a α -lithiohydrazone is a highly carbanionic species and that the reaction with aldehydes may be under chelation control. *N*-Tosyl hydrazone derivatives are readily converted to a dianion and undergo the same type of reactions.²²⁴



Oximes are a useful source of carbanions in aldol-like condensations. Jung et al. showed that oxime **333** reacted with two equivalents of *n*-butyllithium to give the dianion **334**, which reacted with 1-bromopropane.^{225,226} Subsequent treatment with water resulted in a 53% yield of **335**. *O*-Tetrahydropyranyl oximes such as **336** can be used in this sequence, and the fact that the oxygen is blocked removes the necessity for generating a dianion, which may have solubility problems that diminish the yield of subsequent reactions. Conversion of 2-heptanone to the *O*-tetrahydropyranyl oxime produced a 61:39 mixture of (*E/Z*) isomers (**336**). Treatment with LDA followed by condensation with acetone led to a mixture of oximes (**337/338**) in 94% yield, maintaining the 61:39 (*E/Z*) ratio.²²⁷ Warming **336** to -50° C (from -78° C) led

- 223. Corey, E.J.; Enders, D. Tetrahedron Lett. 1976, 11.
- 224. Lipton, M.F.; Shapiro, R.H. J. Org. Chem. 1978, 43, 1409.
- 225. Jung, M.E.; Blair, P.A.; Lowe, J.A. Tetrahedron Lett. 1976, 1439.
- 226. (a) Adlington, R.M.; Barrett, A.G.M. J. Chem. Soc. Chem. Commun. 1979, 1122; (b) Idem Ibid. 1978, 1071.
- 227. Ensley, H.E.; Lohr, R. Tetrahedron Lett. 1978, 1415.

^{220. (}a) Corey, E.J.; Enders, D. Tetrahedron Lett. 1976, 3; (b) Idem Chem. Ber. 1978, 111, 1337.

^{221.} Paterson, I.; Tudge, M. Angew. Chem. Int. Ed., 2003, 42, 343.

^{222.} Corey, E.J.; Enders, D. Chem. Ber. 1978, 111, 1362.

to isomerization, giving exclusively the (*E*)-isomer. When the condensation of (*E*)-**336** with acetone was done at -50° C, a single product (**337**) was obtained.²²⁷



9.4.G. Nozaki-Hiyama-Kishi Coupling

Another acyl addition reaction involves an organochromium intermediate. Although it is not formally an enolate anion condensation, it is related to the acyl addition reactions presented in this chapter. As originally formulated by Nozaki and co-workers, vinyl triflates such as **339** were treated with an aldehyde and CrCl₂ in the presence of a nickel catalyst.²²⁸ Initial formation of a vinyl nickel species was followed by *in situ* transmetalation to give a vinyl Cr(III) species, which added to the aldehyde. Hydrolysis gave the alcohol product. When

339 reacted with benzaldehyde, an 83% yield of **340** was obtained.²²⁸ Kishi and co-workers employed a similar reagent for coupling activated alkenes with aldehydes, during synthetic studies

toward palytoxin,²²⁹ and later work involving the synthesis of taxanes²³⁰ expanded the reaction. Hiyama et al. studied reactions of bromobutenes with aldehydes in the presence of Cr(II) reagents.²³¹ This transformation is the **Nozaki-Hiyama-Kishi reaction**,²³² although it has also been referred to as the **Takai-Utimoto reaction**. Fürstener and Shi employed a Cr(II)-Mn(0) redox couple to give essentially the same coupling reaction.²³³ Boeckman and Hudack used this reagent to prepare anti-diols with high stereoselectivity.²³⁴ A slight modification of

^{228.} Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. J. Am. Chem. Soc. 1986, 108, 6048.

^{229.} Jin, H.; Uenishi, J.; Christ, W.J.; Kishi, Y. J. Am. Chem. Soc. 1986, 108, 5644.

^{230.} Kress, M.H.; Ruel, R.; Miller, L.W.H.; Kishi, Y. Tetrahedron Lett. 1993, 34, 5999.

^{231. (}a) Hiyama, T.; Kimura, K.; Nozaki, H. *Tetrahedron Lett.* 1981, 22, 1037; (b) Hiyama, T.; Okude, Y.; Kimura, K.; Nozaki, H. Bull. Chem. Soc. Jpn. 1982, 55, 561.

⁽a) Cintas, P. Synthesis 1992, 248; (b) Wessohann, L.A.; Scheid, G. Synthesis 1999, 1 (see pp 16-18); (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-67; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 466-467.

^{233.} Fürstner, A.; Shi, N. J. Am. Chem. Soc. 1996, 118, 12349.

^{234.} Boeckman, Jr., R.K.; Hudack, Jr., R.A. J. Org. Chem. 1998, 63, 3524.

this fundamental reaction leads to vinyl iodides. ²³⁵ An intramolecular example, taken from a synthesis of bipinnatin J by Trauner and Reothle, showed that treatment of **341** with $CrCl_2/NiCl_2$ gave **342** (bipinnatin) in 59% yield, with a diastereoselectivity of >9:1.²³⁶



9.5. STEREOSELECTIVE ENOLATE REACTIONS

When a prochiral enolate reacts with an aldehyde or an unsymmetrical ketone to give a aldolate product (**343**), two new stereogenic centers are created (when $R \neq H$). When an enolate reacts



with an alkyl halide, one new stereogenic center is created as in **344** (when $R \neq H$). There have been many advances in the area of asymmetric enolate methodology.²³⁷ The purpose of this section is to discuss those factors that influence diastereoselectivity, and enantioselectivity in alkylation and condensation reactions of enolate anions.

Note that several factors influence both the stereoselectivity of hydrogen exchange and enolate formation in base-promoted reactions. Houk, Ando and co-workers found that differing conjugative stabilization by CH *p*-orbital overlap does not directly influence stereoselectivity.²³⁸ Steric effects dominate only in exceptionally crowded transition structures, but torsional strain involving vicinal bonds contributes significantly to the stereoselectivity of all cases studied.

9.5.A. Simple Diastereoselection

9.5.A.i. Alkylation. If the aldol condensation reaction that produces **344** could be controlled, one diastereomer might be formed in preference to the other, making the reaction diastereoselective. There are two essential factors that control diastereoselectivity in this reaction: the *face* from which the two reagents approach and the relative *orientation* of the two molecules.

^{235.} Lee, K.-Y.; Oh, C.-Y.; Ham, W.-H. Org. Lett. 2002, 4, 4403.

^{236.} Roethle, P.A.; Trauner, D. Org. Lett. 2006, 8, 345.

^{237.} Arya, P.; Qin, H. Tetrahedron 2000, 56, 917.

^{238.} Behnam, S.M.; Benham, S.E.; Ando, K.; Green, N.S.; Houk, K.N. J. Org. Chem. 2000, 65, 8970.

Enolate alkylation with simple aldehydes and ketones does not generally lend itself to enantioselective control due to the planar nature of the enolate π system.²³⁹ Inspection of **345** shows that the *si-re* face (face *a*) has no more steric hindrance than the *re-si* face (face *b*). When this enolate reacts with iodomethane, therefore, no facial selectivity is anticipated and the



methylated product will be racemic at the newly-formed stereogenic center. In general, enolate alkylation reactions produce chiral, racemic products. The reaction can be diastereoselective, however, when substituents attached to the molecule provide facial bias. In general, enolate alkylation proceeds by approach of the enolate to the halide from the less sterically hindered face of the enolate anion. In the Molander and Haas synthesis of davanone,²⁴⁰ ketone **346** was treated with LDA and then with iodomethane. Three products were formed, 58% of **348**, 8% of **349** and <2% of dialkylation product **350**. About 20% of unreacted **346** was recovered. Inspection of the enolate anion formed from **346** (see **347**) shows that the exo face of the bicyclic system is the least hindered for attack of iodomethane, and accounts for the stereochemistry of the methyl group(s) in all three products The regioselectivity for **348** is attributed to formation of the enolate anion and alkylation away from the bridgehead methyl group. Another example is the conversion of **351** to **353** in Paquette and Heidelbaugh's synthesis of xyloside derivatives.²⁴¹ Reaction with LDA led to enolate anion **352**, and reaction with formaldehyde gave hydroxymethyl derivative **353**, with reaction occurring from the less hindered exo face of the enolate anion.



9.5.A.ii. Diastereoselectivity in the Aldol Condensation. Enolate anions react with other carbonyl compounds to give aldol or Claisen condensation products, as discussed in previous sections. An aldol condensation with the enolate of 1-phenyl-1-propanone and benzaldehyde generates two new stereocenters, and gives two racemic diastereomers (four stereoisomers). These two diastereomers are the racemic anti diastereomer (354 and 357), and the racemic

^{239.} Meyers, A.I.; Williams, D.R.; Erickson, G.W.; White, S.; Druelinger, M. J. Am. Chem. Soc. 1981, 103, 3081.

^{240.} Molander, G.A.; Haas, J. Tetrahedron 1999, 55, 617.

^{241.} Paquette, L.A.; Heidelbaugh, T.M. Synthesis 1998, 495.

syn diastereomer (**355** and **356**). Diastereoselectivity in this reaction depends on the reaction conditions and the enolate and aldehyde partners, and this section will explore the origins of diastereoselection. Many aldol products undergo syn-anti isomerization in the presence of imidazole via an enolization mechanism,²⁴² so in some cases the syn-anti ratio can be modified.



Heathcock et al. described processes that formed diastereomers in the aldol condensation, from precursors that do not contain a chiral center, as **simple diastereoselectivity**.^{243,244} Ther naming protocols for the diastereomers produced in the aldol condensation are erythro/threo^{245,246,247,248} and the syn/anti²⁴⁹ (see sec. 1.4.B). The latter convention designates diastereomers **354** and **357** as anti, and diastereomers **355** and **356** as syn.

9.5.A.iii. The Zimmerman-Traxler Model. It would be useful to have a simple model that would predict the major diastereomer produced in an aldol condensation with confidence. In Section 9.2.C, the geometry of the enolate was shown to be important and the geometry could be controlled to some extent. In general, a (Z)-enolate such as **358** will generate a syn diastereomer (**359**). In contrast, an (E) enolate such as **360** will generate the



anti diastereomer (**361**). Once the geometry of the enolate anion has been established, a cyclic transition state model is used to predict diastereoselectivity. The most popular transition state is the closed or chelated transition state,²⁵⁰ first proposed by Zimmerman and Traxler^{250b} for

243. Heathcock, C.H.; White, C.T.; Morrison, J.J.; Van Derveer, D. J. Org. Chem. 1981, 46, 1296.

^{242.} Ward, D.E.; Sales, M.; Sasmal, P.K. J. Org. Chem. 2004, 69, 4808.

^{244.} Heathcock, C.H. in Asymmetric Synthesis Vol. 3, Morrison, J.D. Ed., Academic Press, New York, 1983.

Reference 244, citations 5-14 therein. For example, see (a) Cahn, R.S.; Ingold, C.; Prelog, V. Angew. Chem. Int. Ed. 1966, 5, 385; (b) Noyori, R.; Nishida, I.; Sakata, J.; Nishizawa, M. J. Am. Chem. Soc. 1980, 102, 1223; (c) Evans, D.A.; Vogel, E.; Nelson, J.V. Ibid. 1979, 101, 6120; (d) Seebach, D.; Golinski, J. Helv. Chim. Acta 1981, 64, 1413; (e) Seebach, D.; Prelog, V. Angew. Chem. Int. Ed. 1982, 21, 654.

^{246.} Winstein, S.; Lucas, H.J. J. Am. Chem. Soc. 1939, 61, 1576, 2845.

^{247. (}a) Lucas, H.J.; Schlatter, M.J.; Jones, R.C. J. Am. Chem. Soc. 1941, 63, 22; (b) Cram, D.J. Ibid. 1952, 74, 2149; (c) Curtin, D.Y.; Kellom, D.B. Ibid. 1953, 75, 6011; (d) House, H.O. Ibid. 1955, 77, 5083.

^{248. (}a) Eliel, E.L. *Stereochemistry of Carbon Compounds*, McGraw Hill, New York, **1962**; (b) Mislow, K. *Introduction to Stereochemistry*, W.A. Benjamin, New York, **1965**.

^{249.} Masamune, S.; Ali, Sk.A.; Snitman, D.L.; Garvey, D.S. Angew. Chem. Int. Ed. 1980, 19, 557.

^{250. (}a) Reference 244, p 154; (b) Zimmerman, H.E.; Traxler, M.D. J. Am. Chem. Soc. 1957, 79, 1920.

the Ivanov condensation of phenylacetic acid and benzaldehyde. The **Ivanov condensation**²⁵¹ treats a carboxylic acid with an excess of a Grignard reagent to give a bis(magnesium) ketene acetal (**362**).^{251a} Subsequent reaction with a carbonyl compound (benzaldehyde) led to an aldol-like product (**363**). The cyclic model proposed to describe the Ivanov reaction (model **364**) can be used for aldol condensations, if magnesium is replaced with lithium to give cyclic model **365**. When **365** is used to predict stereochemistry in the aldol condensation, it is referred to as the **Zimmerman-Traxler model**.²⁵⁰



There is *no* evidence that the Zimmerman-Traxler model represents the actual transition state for aldol-like reactions. Nonetheless, this model is an extensively used mnemonic that makes reasonable predictions in many cases. It is used to predict structure-selectivity relationships for lithium, boron, zinc or magnesium enolates when they react with aldehydes and ketones. There are four possible transition states, indicated by for an aldol condensation (366, 367, 368, and 369), reflecting the different orientations of enolates with respect to the aldehyde (or ketone), as well as the (E/Z) geometry of the enolate. For simplicity, approach of the aldehyde to the enolate from a single face²⁵² is shown in all cases (the back face is shown, as well as the front face), and the reaction generates enantiomers.



^{251. (}a) Ivanoff, D.; Spassoff, A. Bull. Chim. Soc. Fr. 1931, 49, 19; (b) Ivanoff, D.; Mihova, M.; Christova, T. Ibid. 1932, 51, 1321; (c) Ivanoff, D.; Nicoloff, N.I. Ibid. 1932, 51, 1325, 1331; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-47; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 342-343.

^{252.} Reference 244, p 155.



Referring to these generalized models, when R^2 is small, the chair transition state explains the stereochemical trend. For (*Z*)-enolates, the $R^1 \leftrightarrow R^3$ interaction dominates, and **366** is favored over **367** as the steric bulk increases, leading to more of the syn isomer. For (*E*) enolates, the $R^1 \leftrightarrow R^3$ interaction favors **368** over **369**, and the anti aldolate is the major product.





Model **370** is shown for transition state **366**, for the specific condensation of benzaldehyde ($R^3 =$ Ph) with the (*E*)-enolate of 2-butanone ($R = R^2 =$ Me). A similar model (**371**) is shown for the opposite orientation (transition state **367**). These representations are not the true transition states, but they show the pseudo-axial and pseudoequatorial interactions of the phenyl and methyl

groups for the condensation of benzaldehyde with the thermodynamic enolate of 2-butanone. Transition states **366** and **367** represent the generalized reaction with a (Z)-enolate with an aldehyde for two different orientations. For the (E)-enolate, the steric interactions in **367** (see **371**) appear to be greater than those in **366** (see **370**) due to the pseudo-equatorial phenyl and methyl groups in **367** (**371**). In **366**, one group is pseudo-axial and the other is pseudo-equatorial, minimizing the steric interaction.

Transition state **366** would be used to predict the major product of the aldol reaction, where the (*E*)-enolate predicts the syn-diastereomer. Model **372** represents **368** and **373** represents **369** as transition states for the reaction of benzaldehyde with the (*Z*) enolate of 2-butanone. Pseudo-diaxial groups in **372** (**368**) have minimal steric interactions. Conversely, the pseudo-

diequatorial placement of the phenyl and methyl groups in **373** (**369**) brings those groups into relatively close proximity. Transition state **368** is therefore lower in energy, and predicts the anti diastereoselectivity of the final product. Using the Zimmerman-Traxlermodel for the benzaldehyde-2-butanone system, transition state **374** for this



system predicts the initial aldolate product (375) and the final syn product, 376. Similarly, the (Z) enolate uses transition state 377 to give the aldolate product (378) and the final anti product 379.



Identical conclusions can be drawn when the Zimmerman-Traxler model is applied to ester enolates. The (*Z*) enolate **380** (derived from the corresponding ester in Table 9.10) reacted with various aldehydes to give a mixture of the anti **381** and the syn (**382**) product, with the anti product predominating.²⁵³

Table 9.10. The Syn/Anti Selectivity of Ester Enolates with Benzaldehyde²⁵³

$R^2 \downarrow OR^1 \xrightarrow{LDA} R^2$	O ⁻ Li ⁺ <u>F</u> OR ¹	$R^{3}CHO$ R^{3} R^{3} R^{3} R^{3} R^{3}	$\bigcup_{r=1}^{O} OH OH R^{2}$	O ↓ OR ¹ 2 382
$\mathbf{R}^{\underline{1}}$	<u>R²</u>	<u>R³</u>	<u>381 : 382</u>	
Me	Me	Me	57:43	
		Ph	55:45	
		<i>i</i> -Pr	55:45	
CH ₂ OMe	Me	Me	67:33	
		<i>i</i> -Pr	90:10	
DMP ^a	Me	Ph	88:12	
		<i>n</i> -C ₅ H ₁₁	86:14	
		<i>i</i> -Pr	>98 : 2	
		<i>t</i> -Bu	>98 : 2	
^a DMP = 2,6-dimethylphenyl	Et	<i>i</i> -Pr	>98:2	

253. Reference 244, pp 123-124.

A similar model has been applied to aldol condensation reactions of boron enolates.²⁵⁴ The reaction of (*E*) enolate **383**, for example, can lead to either transition state **385** or **386**. Transition state **385** generates the threo (anti) diastereomer **389**. Transition state **386** leads to the erythro (syn) aldolate **390**. Likewise, (*Z*)-enolate **384** has two transition states, **387** and **388**. Transition state **387** leads to the anti- diastereomer (**389**), and **388** leads to the syn diastereomer **390**. With lithium enolates (M = Li), the reaction is diastereoselective if R¹ is sterically demanding (e.g., R = tert-butyl). When R¹ is relatively small, the diastereoselectivity is diminished. Examining boron enolates shows the B–O bond to be shorter than the O–Li bond, which maximizes stereocontrol in a kinetic aldol process. The (*Z*)-enolate **388** is the lowest energy pathway. When R¹ is *tert*-butyl (**384**, L = butyl), the preference for the syn diastereomer, **392**.²²³ This result clearly suggests transition state **388** is the lowest energy pathway. When R¹ is *tert*-butyl (**384**, L = butyl), the preference for the syn diastereomer was >97:1. For cyclohexanone enolate **393** (locked into the (*E*) geometry), the reaction with benzaldehyde gave primarily the anti diastereomer (**394**, 33:67 syn/anti).²⁵⁴ A Zimmerman-Traxler-like model also is useful for predicting the diastereoselection in boron enolates as well as lithium enolates.



254. Evans, D.A.; Vogel, E.; Nelson, J.V. J. Am. Chem. Soc. 1979, 101, 6120.

9.5.A.iv. The Evans' Model. (*Z*) Enolates are more stereoselective than (*E*) enolates, even when R¹ is not large. The Zimmerman-Traxler model transition states **366-369** do not account for this observation. It has been suggested that the transition states are not chair-like, but skewed as in **395-398**.²⁵⁵ In this representation, (*Z*) enolate **395** leads to the syn aldolate. Similarly, (*Z*) enolate **396** gives the anti aldolate, (*E*) enolate **397** gives the anti aldolate. The major steric interactions in this model are those for R¹ \leftrightarrow R³ and R² \leftrightarrow R³. For both (*Z*) and (*E*) enolates, the R¹ \leftrightarrow R³ interaction favors **395** and



397, respectively. The $R^2 \leftrightarrow R^3$ interaction is more important for the (*E*) enolate and leads to **396** and **398** when R^1 is large. The angle at which the reagents approach is obviously important for these transition states. It is assumed that the angle of attack of a nucleophile is 110° as it attacks a carbonyl (sec. 6.6.A), the **Bürgi-Dunitz trajectory** (sec. 9.2.D).¹¹ This angle of attack brings R^2 and R^3 in **397** into close proximity and relieves the $R^1 \leftrightarrow R^3$ interaction. Similar results are observed for **396** and **398**, but to a lesser degree, which explains why (*E*) enolates show comparable $R^2 \leftrightarrow R^3$ and $R^1 \leftrightarrow R^3$ interactions unless R^1 is very large, and also accounts for the large effect of the R^2 group on the diastereoselectivity. As R^2 increases in size, transition states **395** and **397** become less important.



Evans et al. considered boat conformations $399-402^{256}$ as possible transition states, in addition to the chair conformations used in the Zimmerman-Traxler model. In these boat conformations, reaction of an aldehyde with (*Z*) enolate via orientation **399** gives the syn aldolate, but reaction via the opposite orientation of the aldehyde (see **400**) gives the anti aldolate. Likewise, reaction of an aldehyde with (*E*) enolate via the orientation shown in **401** gives the anti aldolate, whereas the opposite orientation (see **402**) gives the syn aldolate. A given (*Z*) or (*E*) enolate, therefore, has one or two chair transition states,

or one or two boat transition states that are energetically favorable for an aldol condensation. Only transition states **400** and **401** are considered important, because of the significant $R^2 \leftrightarrow R^3$ interactions in **399** and **402**. As R^2 becomes larger, however, the (*Z*) enolate might favor **400**

^{255. (}a) Heathcock, C.H. Comprehensive Carbanion Chemistry Vol. 2, Durst, T.; Buncel, E. Eds., Elsevier, Amsterdam, 1985; (b) Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.A.; Sohn, J.E.; Lampe, J. J. Org. Chem. 1980, 45, 1066; (c) Fellmann, P.; Dubois, J.E. Tetrahedron 1978, 34, 1349; (d) Dubois, J.E.; Fellmann, P. Tetrahedron Lett. 1975, 1225.

^{256.} Evans, D.A.; Nelson, J.V.; Taber, T.R. Topics in Stereochemistry 1982, 13, 1.

or the chair transition state. Boat transition states predict that increasing the steric bulk of R² in an (E) enolate will either have no effect on stereochemistry or increase selectivity for the anti aldolate. There is some evidence for a modest increase in anti selectivity with increasing the size of R².²⁵⁷

9.5.A.v. The Noyori Open-Chain Model. In the Mukaiyama reaction, the Zimmerman-Traxler and Evans' models are not satisfactory for predicting diastereoselectivity. Several open (nonchelated) transition states have been considered as useful models. The condensation reaction of carboxylic acid dianions with aldehydes indicated that anti selectivity increased with increasing dissociation of the gegenion (the cation, M⁺).²⁵⁸ When analyzing an aldol condensation that does not possess the bridging cation required for the Zimmerman-Traxler model, an aldehyde and enolate adapt an eclipsed orientation as they approach. Noyori reported syn selectivity for the reaction of a mixture of (Z)-silyl enol ether 403 and (E)-silyl enol ether 404 with benzaldehyde, in the presence of the cationic reagent tris(diethylamino) sulfonium (TAS).²⁵⁹ This reaction is clearly a variation of the Mukaivama reaction, which usually proceeds with poor diastereoselectivity (sec. 9.4.C). The reaction of the (Z) enolate 403 and the (E)enolate (404), led to formation of 405 as the major product. The 86:14 (405/406) preference²⁶⁰

$$C_{3}H_{7} \underbrace{\downarrow}_{n-C_{4}H_{9}} + \underbrace{\downarrow}_{C_{3}H_{7}} \underbrace{\downarrow}_{n-C_{4}H_{9}} \underbrace{\downarrow}_{n-C_{4}$$

for the syn diastereomer was independent of the enolate geometry. These results are predicted with the open-chain model. The (Z) enolate will form a transition state such as 407, which



leads to the anti diastereomer. The significant $R^2 \leftrightarrow R^3$ interaction that

destabilizes that transition state. This does not explain why both (E- and (Z) enolates lead to the syn-diastereomer (405), and some equilibration or isomerization must occur during the course of the reaction, which will be discussed in Section 9.5.A.vi.



^{257.} Reference 244, p 151.

^{258.} Mulzer, J.; Zippel, M.; Brüntrup, G.; Segner, J.; Finke, J. Liebigs Ann. Chem. 1980, 1108.

Noyori, R.; Yokoyama, K.; Sakata, J.; Kuwajima, I.; Nakamura, E.; Shimizu, M.J.Am. Chem. Soc. 1977, 99, 1265. 259.

^{260.} Novori, R.; Nishida, I.; Sakata, J. J. Am. Chem. Soc. 1981, 103, 2106.

9.5.A.vi. Isomerization in the Aldol Condensation. It is clear from the previous discussion that steric effects control the orientation of the molecule as it approaches the enolate anion. In simple diastereoselection processes, one observes moderate to good syn/anti selection depending on the steric demands of the enolate and carbonyl partner. However, other processes are at work in this condensation that lead to variations in the syn/anti ratio. Heathcock reported the selectivity for a variety of lithium enolates derived from **409** with benzaldehyde (see Table 9.11).^{28,261} The (*E*) and (*Z*) enolates (**411** and **410**, respectively) can be trapped with trimethylsilyl chloride to give silyl-enol ethers **413** and **412**, respectively. The observed **412/413** ratio is taken to be the ratio of (*Z*) and (*E*)-enolates originally generated from **419**. When the enolate mixture reacted with benzaldehyde, the syn aldolate **414** and the anti aldolate **415** were formed.²⁶¹ It is clear from Table 9.11 that the (*E/Z*) enolate ratio (taken to be **414/415**) is not the same as observed in the aldolate products. One explanation is that the enolate anions equilibrate under the reaction conditions. Isomerization may occur during or after the aldolate-forming step, and the enolate ratio may be the same but the aldehyde adds from different faces of the enolate anion (see above).

100 R - 409	base -78°C ► Me	∼~ ^R + 0 [−] Li ⁺ 410	Me $\sim R^{O^-Li^+}$ 411	$\frac{\text{Me}_3\text{SiCl}}{1.\text{ PhCHO}}$ $\frac{1.\text{ PhCHO}}{2.\text{ H}_3\text{O}^+}$	Me 412 OS OH → Ph 414 M	R + Me SiMe ₃ + Me	$\begin{array}{c} & OSiMe_3 \\ R & 413 \\ OH & O \\ h & R \\ 415 & Me \end{array}$
R	Base	<u>412 : 413</u>	<u>414 : 415</u>	R	Base	<u>412 : 413</u>	<u>414 : 415</u>
LiO	LDA		45 : 55	<i>i</i> -Pr	LDA	60:40	82:18
MeO	LDA	5:95	62:38		LICA	59:41	75:25
t-BuO	LDA	5:95	49:51		LHMDS	>98:2	90:10
<i>i</i> -Pr ₂ N	LDA	81:19	63 : 57		LTMP	32:68	58:42
	LTMP	52:48	68:32	<i>i</i> -Bu	LDA	>98:2	>98:2
Н	MeLi	100:0	50:50		LHMDS	>98:2	>98 : 2
		0:100	65:35	Ph	LDA	>98:2	88:12
Et	LDA	30:70	64 : 36		LICA	>98:2	87:13
	LICA	35:65	62:38		LHMDS	>98:2	88:12
	LHMDS	66 : 34	77:23		LTMP	>98:2	83:17
	LTMP	20:80	66 : 34				
LDA = lithium diisopropylamide LHMDS = lithium hexamethyldisilazide LTMP = lithium tetramethylpiperidide							
[Reprinted with permission from Heathcock, C.H.; Buse, C.T.; Kleschick, W.A.; Pirrung, M.A.; Sohn, J.E.; Lampe, J. J. Org. Chem. 1980, 45, 1066. Copyright © 1980 American Chemical Society.]							

 Table 9.11. Stereoselectivity in Enolate Formation and Diastereoselectivity in the Aldol Condensation

The nature of the amide base had a substantial effect on the (E/Z) ratio of the enolate. In general, LTMP gave mainly the (E) enolate and LHMDS the (Z) enolate, which is probably related to the aggregation state of the base. As the size of R increases, the use of LTMP and LDA increases

^{261.} Reference 244, pp 122-132.

the amout of (*Z*) enolate, which is related to the conformation of the ketone immediately prior to deprotonation, using the Felkin-Anh model (sec. 4.7.B). Conformation **416** is more stable than **418** for propanal by 0.8 kcal mol⁻¹ (3.35 kJ mol⁻¹).²⁶² This difference is probably greater in ketones (R = alkyl or aryl) and esters (R = O-alkyl). This observation suggests that as R becomes larger the (*Z*) enolate is preferred, regardless of the base. The observation that LTMP gives more (*E*) enolate can be explained by a steric interaction between the base and the methyl group (see **416**). The methyl \leftrightarrow R interaction is greater, but the interaction of the methyl group and the base is minimized in **419**, This model assumes approach of the base and ketone is not along the axis of the C–H bond, but over the face of the incipient enolate plane.²⁶³ With benzaldehyde, (*E*) and (*Z*) enolates may exhibit different degrees of stereoselectivity.



The results in Table 9.11 can be explained by the Zimmerman-Traxler-like transition state (420). The $R^2 \leftrightarrow R^5$ and $R^1 \leftrightarrow R^4$ interactions are very important. When R^5 is large (such as



adamantyl) the (Z) enolate gives the syn aldolate, and the (E) enolate the anti aldolate. When R^5 is small (Ph, Et), the (Z) enolate gives primarily the syn aldolate. When $R^5 = H$, reactions of the (Z) enolate become stereorandom and lead to diastereomeric mixtures of products. When R^5 is small (Ph, Et), the (E) enolate usually gives a 50:50 mixture of syn and anti aldolates, probably because the $R^1 \leftrightarrow R^4$ interaction balances the

 $R^2 \leftrightarrow R^5$ interaction. When $R^5 = H$ or Me, the (E) enolate is selective for the syn diastereomer.

A complicating factor is the observation that aldolates can undergo syn/anti equilibration by enolization or by reverse aldolization. Aldolates such as **421** can be deprotonated to the dianion (**422**), which undergoes alkylation with iodomethane to give the anti product (**423**), as shown.²⁶⁴ This equilibration is clearly the basis of the aldol-transfer reaction discussed in **152** to **154** in Section 9.4.A.i. If **423** forms a new enolate, equilibration can lead to a mixture of syn and anti products. The primary mechanism for syn/anti equilibration appears to be reverse aldolization.²⁶⁵ A retro-aldol condensation will convert the syn diastereomer (**424**) into the aldehyde and enolate components, which can regenerate **424** or form the anti diastereomer **425**.

^{262.} Karabatsos, G.J.; Hsi, N. J. Am. Chem. Soc. 1965, 87, 2864.

^{263. (}a) Ireland, R.E.; Willard, A.K. *Tetrahedron Lett.* **1975**, 3975; (b) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Ibid.* **1978**, 2079.

^{264. (}a) Fráter, G. Helv. Chim. Acta 1979, 62, 2825, 2829; (b) Seebach, D. Wasmuth, D. Ibid. 1980, 63, 197.

^{265.} Reference 244, pp 161-162.



Syn/anti equilibration can be much slower than reverse aldolization, as with the (Z) enolate of 2,2-dimethyl-3-pentanone).²⁶¹ Aldolates derived from the more basic ketone enolates are more likely to suffer reverse aldolization than aldolates derived from the less basic enolates of esters, amides or carboxylate salts. Steric crowding in an aldolate promotes reverse aldolization. The metal is very important, and some metals form stable chelates that generate aldolates resistant to reverse aldolization. Boron enolates, for example, do not undergo equilibration even at elevated temperatures. Lithium enolates equilibrate more slowly than other alkali metal enolates and potassium enolates equilibrate rapidly.

9.5.B. Selectivity with Chiral, Nonracemic Reactants

9.5.B.i. Diastereoface Selectivity^{243,266} Heathcock defined three kinds of stereoselection for the aldol condensation: simple diastereoselection, diastereoface selection, and double stereodifferentiation.^{243,258} Simple diastereoselection occurred when an achiral aldehyde and an achiral ketone reacted to give a mixture of syn and anti aldol products **426** and **427**. This example illustrates the type of reaction discussed previously.

$$R-CHO + \underbrace{O}_{R^{1}} \xrightarrow{base} \underbrace{H_{3}O^{+}}_{Me} R \xrightarrow{OH O}_{Me} R^{1} + R \xrightarrow{OH O}_{F} R^{1}$$

If either the enolate or carbonyl partner has a stereogenic center near the reactive center, it will influence both orientation and facial selectivity.^{243,255} Reaction of an achiral enolate such as **429** with an aldehyde or a ketone that possesses a (\underline{S}) stereogenic center (**428**) will give the (*SRS*) diastereomer (**430**) and the (\underline{SRR}) diastereomer (**431**) aldolate products. The (S) stereogenic center in **428** can induce high diastereoselectivity, with **430** as the major product. An aldehyde with a (R) stereocenter will similarly influence the reaction, giving **431** as the major aldolate product. Several factors influence the extent of diastereoselectivity. A second variation reacts an enolate possessing a stereogenic center (such as **432**) with an achiral aldehyde or ketone.

^{266.} Also see (a) White, C.T.; Heathcock, C.H. J. Org. Chem. **1981**, 46, 191; (b) Heathcock, C.H.; Young, J.P.; Hagen, M.C.; Pirrung, M.C.; White, C.T.; VanDerveer, D. J. Org. Chem. **1980**, 45, 3846.

In (<u>*R*</u>)-432, the reaction with an aldehyde leads to the (*RS<u>R</u>*) diastereomer 433 and the (*SR<u>R</u>*) diastereomer, 434.



Double stereodifferentiation²⁶⁷ results from the reaction of an enolate possessing a stereogenic center and an aldehyde or ketone that also has a stereogenic center. An example, taken from Calter and Liao's synthesis of siphonarienedione,²⁶⁸ condensed chiral aldehyde **435** with enolate anion **436**. Here, stereoisomer **437** was produced in 65% yield as a result of double stereodifferentiation.

$$H \xrightarrow{O}_{\underline{i}} C_{3}H_{7} \xrightarrow{Me}_{MeO} \xrightarrow{O}_{\underline{i}} C_{1}H_{7} \xrightarrow{O}_{MeO} \xrightarrow{O}_{\underline{i}} C_{1}H_{7} \xrightarrow{I. THF/CH_{2}Cl_{2}}{I. H_{3}O^{+}} Me \xrightarrow{O}_{OMe} \xrightarrow{O}_{\underline{i}} \xrightarrow{O}_{\underline{i}} \xrightarrow{O}_{\underline{i}} C_{3}H_{7} \xrightarrow{C}_{3}H_{7}$$

Improvements in diastereoselection arise from factors that influence the orientation of the reaction, and the face from which the two reactants approach. For simple diastereoselectivity, steric factors influence the orientation of the aldehyde and enolate, leading to good syn/anti selectivity using the models previously described. When a stereogenic center is incorporated in the enolate or aldehyde, increased steric hindrance affects the approach and transition state energies, leading to greater diastereoselectivity. The presence of the stereogenic center makes one face of the molecule more hindered than another when comparing the possible transition states, and a preference for one over another is called facial selectivity. As observed in Table 9.12,²⁶⁹ when an aldehyde possessing a stereogenic center (such as **438**) was condensed with various enolate anions (**439**), the syn-diastereomer (**440**) predominated over the anti-diastereomer (**441**) in every case.

^{267. (}a) Horeau, A.; Kagan, H.-B.; Vigneron J.-P. Bull. Soc. Chim. Fr. 1968, 3795; (b) Izumi, Y.; Tai, A. Stereodifferentiating Reactions, Kodanshar Ltd., Tokyo, Academic Press, New York, 1977.

^{268.} Calter, M.A.; Liao, W. J. Am. Chem. Soc. 2002, 124, 13127.

^{269.} Reference 244, p 166.

Me Ph CHO + 438	$\stackrel{O^-M^+}{\underset{R}{\longrightarrow}} \stackrel{TH}{}$	$\xrightarrow{\text{H}_3\text{O}^+}$	$Ph \underbrace{\overset{Me}{\overbrace{OH}}_{OH}^{(syn)}}_{H} R$	+ $Ph \xrightarrow{Me (anti)}_{OH O} R$ 441
<u>R</u>	M	<u>Temp. (°C)</u>	<u>440 : 441</u>	<u>% Yield</u>
MeO	ZnBr	80 (in PhH)	74:26	78
MeO	Li	-78	75:25	91
t-BuO	Li	-78	80:20	70
Me	Li	-78	76:24	98
Me	$c - (C_5 H_9)_2 B$	0	65:35	
<i>t</i> -Bu	Li	-78	80:20	80
Me ₂ N	Li	-78	78 : 22	67

 Table 9.12. Influence of an Asymmetric Aldehyde on Facial Selectivity in the Aldol Condensation with a Metal Enolate

In most cases, Crams rule (sec. 4.7.B) predicts the major isomer if the reaction partner (or partners) contain a stereogenic center.²⁷⁰ To understand how this rule applies to orientational and facial selectivity, we must understand the transition state of the reaction. The Zimmerman-Traxler model is used most often, and if it is applied to **438** and **439**, the syn selectivity can be predicted. The facial selectivity shown in **442** and **443** arises from the methyl group. In **443**, the enolate approaches from the face opposite the methyl, leading to diminished steric interactions and syn product (**444**). If the enolate approaches via **442**, the steric impedance of the methyl group destabilizes that transition state relative to **443**. In both **442** and **443**, a Cram orientation is assumed (see above), although other rotamers are possible. The appropriate rotamer for reaction is that where R_L is anti to the carbonyl oxygen. Since the phenyl group is R_L , **442** and **443** are assumed to be the appropriate orientation for the aldehyde. If an aldehyde or ketone follows anti-Cram selectivity, this aldehyde orientation must be adjusted.



Cram selectivity (sec. 4.7.B) results from approach of the enolate over the less hindered face of the stereogenic center of the aldehyde (over the H, R_s) rather than over the larger methyl group (R_M). The phenyl group is taken to be R_L , and it is anti to the carbonyl oxygen. This model assumes a reasonable steric difference between R_M and R_s (as in the Cram model), and if the steric difference between the two groups is small, there is little facial selectivity in the transition state and poor enantioselectivity in the final product.

^{270. (}a) Cram, D.J.; AbdElhafez, F.A. J. Am. Chem. Soc. 1952, 74, 5828; (b) Cram, D.J.; Kopecky, K.R. Ibid. 1959, 81, 2748.

The presence of a stereogenic center in the enolate imparts facial selectivity, and reaction of (*S*)-3-methyl-2-pentanone (**445**) was treated with LDA, chiral enolate **446** was formed.²⁷¹ Subsequent reaction with propanal gave the aldolates with a slight preference (57:43 to 63:36) for the anti (*S*,*R*) isomer (**447**) over the syn (*S*,*S*) isomer (**448**). Once again, the methyl group induced a facial bias in the approach of the reagent, leading to attack on the face opposite the

methyl. The results were similar for both lithium and boron enolates. If the transition states for the boron enolates are examined (449 and 450),²⁷² the observed facial bias favors 449 as the least hindered transition state, *assuming an orientation of* R_L *in the transition state according to Cram's rule*, which leads to a preference for the (*S*,*R*) product.



448

Diastereoface selection is observed when a chiral auxiliary is attached to either the enolates or the carbonyl substrate. A chiral auxiliary is an asymmetric group attached to an achiral substrate. The chirality of the auxiliary influences the course of the reaction (an aldol condensation) by inducing a chiral transition state, which influences the chirality of the final product. The auxiliary is cleaved to give the normal aldolate product. Oppolzer et al. developed a sulfonamide alcohol auxiliary based on camphor (**Oppolzer's sultam**) in which an acid derivative is attached as a chiral ester.²⁷³ The auxiliary was removed by reduction of the ester group with LiAlH₄. A related sultam auxiliary also gave good results. In Mori's synthesis of (1*S*, 3*S*, 7*R*)-3-methyl- α -himachalene,²⁷⁴ the sex pheromone of the sand fly *Lutzomyia longipalpis*, amide **451** was prepared from the appropriate acid chloride and Oppolzer's sultam.²⁷⁵ Treatment with butyllithium and iodomethane gave an 81% yield of **452**, and subsequent removal of the auxiliary by basic hydrolysis gave **453** in 67% yield and >99% ee.

EtCHO

447

 $O^- M^+$

446



^{271.} Seebach, D.; Ehrig, V.; Teschner, M. Liebigs Ann. Chem. 1976, 1357.

- 272. Evans, D.A.; Taber, T.R. Tetrahedron Lett. 1980, 21, 4675.
- 273. Oppolzer, W.; Dudfield, P.; Stevenson, T.; Godel, T. Helv. Chim. Acta 1985, 68, 212.
- 274. Tashiro, T.; Bando, M.; Mori, K. Synthesis 2000, 1852.
- 275. Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. Helv. Chim. Acta 1985, 68, 2100.

445

In Leahy and co-worker's synthesis of rhizoxin D, a so-called **Evans' auxiliary** (the chiral, substituted oxazolidinone unit) was used in **454**.²⁷⁶ Generation of the enolate anion with sodium hexamethyldisilazide was followed by reaction with allyl bromide to give a 73% yield of **455**. Helmchen and co-workers²⁷⁷ achieved good asymmetric induction in the alkylation of ester enolates using a camphor based sulfonamide auxiliary.



MOLECULAR MODELING: Enolates that Hold Onto Metals

Up to this point, molecular modeling problems relating to enolate anions have not considered the possible role of the metal counterion. Were the metal to remain attached to an enolate, it could coordinate with other electron-rich centers and restrict conformational freedom. The net effect would be to limit the range of shapes available to the enolate, making it much easier to anticipate the product of electrophilic addition. For example, the conformational flexibility of compound **A** would be greatly reduced upon enolization to **B**, were the lithium to remain and coordinate with the carbonyl oxygen on the oxazolidinone ring.



Metal complexation might also be expected to affect the steric demands of the free enolate, perhaps changing the favored direction of approach of an electrophile. Examine space-filling models for the free and lithium-complexed enolates (top left and right). Is one face of the free enolate more crowded than the other face? Is there a clear "steric" preference for one product over the other? If there is, does this preference lead to the observed product? Does your conclusion change for the lithium-complexed enolate?

What effect does "holding onto to metal" have on the reactivity of an enolate anion. Is the lithiumcomplexed enolate **B** likely to be more or less susceptible to attack by an electrophile than the corresponding free enolate? Compare the local ionization potential map for the free enolate (bottom left) with that of the corresponding lithium complex **B** (bottom right). The maps are displayed as transparent models in order for to see the structure underneath. After you have oriented yourself, you can switch to solid models. *Click* on the map and select *Solid* from the **Style** menu at the bottom of the screen. Recall that the lower the local ionization potential (colored "red" in the map), the more likely the molecule will undergo reaction with the electrophile. According to the local ionization potential maps, is the free enolate or its lithium complex more reactive?

^{276.} Lafontaine, J.A.; Provencal, D.P.; Gardelli, C.; Leahy, J.W. J. Org. Chem. 2003, 68, 4215.

^{277.} Schmierer, R.; Grotemeier, G.; Helmchen, G.; Selim, A. Angew. Chem. Int. Ed. 1981, 20, 207.

Using a chiral additive often generates a reactive species that functions as a transient auxiliary, and constitutes another method for inducing enantioselectivity in aldol-like reactions. Koga and co-workers²⁷⁸ reacted the achiral ketone acetophenone with a chiral, nonracemic base (**456**) in the presence of *N*,*N*,*N'*,*N'*-tetramethylenediamine (TMEDA), to form an enolate coordinated chiral complex. Reaction of this complex with benzaldehyde at -100° C led to asymmetric induction in the final aldolate product (**457**), which was produced in 73% yield with high enantioselectivity for the (*R*)-enantiomer.²⁷⁸ List and Notz showed that the addition of 30 mol% of L-proline induced an asymmetric aldol condensation between hydroxyacetone and cyclohexanecarboxaldehyde to give **458** in 60% yield, with >20:1 regioselectivity, >20:1 diastereoselectivity and >100:1 enantioselectivity.²⁷⁹ The use of chiral Lewis bases in the aldol reaction has been reviewed,²⁸⁰ as have catalytic aldol reactions.²⁸¹



The presence of a chiral auxiliary can influence the stereochemistry of products formed in a Mukaiyama aldol reaction. A stereogenic center derived from a chiral amino alcohol was incorporated in the enol ether moiety (see **459**). When reacted with benzaldehyde and TiCl₄, the alcoholate products were **460** and **461** (R* = the chiral auxiliary). The diastereoselectivity was quite good (95:5 favoring **460**), and each product was formed with high enantioselectivity.²⁸² It is also possible to incorporate the stereogenic center into the starting material (a **chiral template**, as discussed in sec. 10.9).²⁸³

^{278.} Muraoka, M.; Kawasaki, H.; Koga, K. Tetrahedron Lett. 1988, 29, 337.

^{279.} Notz, W.; List, B. J. Am. Chem. Soc. 2000, 122, 7386.

^{280.} Denmark, S.E.; Stavenger, R.A. Acc. Chem. Res. 2000, 33, 432.

^{281.} Machajewski, T.D.; Wong, C.-H. Angew. Chem. Int. Ed. 2000, 39, 1352.

^{282.} Gennari, C.; Molinari, F.; Cozza, P.; Oliva, A. Tetrahedron Lett. 1989, 30, 5163.

^{283.} Woodward, R.B.; Logusch, E.; Nambiar, K.P.; Sakan, K.; Ward, D.E.; Au-Yeung, B.-W.; Balaram, P.; Browne, L.J.; Card, P.J.; Chen, C.H.; Chênevert, R.B.; Fliri, A.; Frobel, K.; Gais, H.-J.; Garratt, D.G.; Hayakawa, K.; Heggie, W.; Hesson, D.P.; Hoppe, D.; Hoppe, I.; Hyatt, J.A.; Ikeda, D.; Jacobi, P.A.; Kim, K.S.; Kobuke, Y.; Kojima, K.; Krowicki, K.; Lee, V.J.; Leutert, T.; Malchenko, S.; Martens, J.; Matthews, R.S.; Ong, B.S.; Press, J.B.; Rajan Babu, T.V.; Rousseau, G.; Sauter, H.M.; Suzuki, M.; Tatsuta, K.; Tolbert, L.M.; Truesdale, E.A.; Uchida, I.; Ueda, Y.; Uyehara, T.; Vasella, A.T.; Vladuchick, W.C.; Wade, P.A.; Williams, R.M.; Wong, H.N.-C. J. Am. Chem. Soc. 1981, 103, 3210.



9.5.B.ii. Double Stereodifferentiation. Double stereodifferentiation employs a stereogenic center on both the enolate and the aldehyde or ketone (see 435 above). The two reactants may have incipient chirality, but the nature of the stereogenic centers lead to a lower energy transition state during the reaction (consonant double stereodifferentiation, matched). Alternatively, that chirality can lead to a higher energy transition state (dissonant double stereodifferentiation, mismatched).^{257,284} This concept of matched and mismatched was introduced in the discussion of the Sharpless asymmetric epoxidation in section 3.4.D.i. The reaction of chiral ketone 462 with LDA generates the corresponding enolate anion, and subsequent reaction with benzaldehyde occurs with high selectivity for the syn isomer (463 rather than 464).



This reaction demonstrates the incipient selectivity of an aldol condensation with chiral ketone **465**. If we replace benzaldehyde with chiral aldehydes, we have an example of matched versus mismatched reactions in an aldol condensation. The condensation of (*R*)-aldehyde **465** or the S aldehyde **470** with enolates derived from ketone **463** is illustrative.^{284,243} When **463** reacted with the mismatched aldehyde **466**, the selectivity was poor due to dissonance in the transition state, with formation of a 62:38 mixture of **467** and **468**. Some anti diastereomers were also produced, which is quite different from the reaction of **462** with **470**, the matched aldehyde. Consonant stereodifferentiation led to excellent selectivity for a single isomer (**471**), produced in > 97% yield. The steric effects of the consonance versus the dissonance approach can be described in terms of the generalized Zimmerman-Traxler models **472** and **473**. In **472**, the R and R² groups are oriented away from each other (matched), minimizing the steric interaction. In **473**, however, the R \leftrightarrow R² interaction is maximized (mismatched), destabilizing that transition state.



^{284.} Heathcock, C.H.; White, C.T. J. Am. Chem. Soc. 1979, 101, 7076.



This selectivity is seen in the condensation of chiral aldehyde **474** with the chiral enolate anion **475**. The matched transition state has the methyl groups oriented away from each other, which is lower in energy than the opposite case in which the methyl groups interfere with each other (both options assume a Cram orientation). The matched orientation predicts formation of the anti diastereomer **476** for this reaction, as shown.



When applied to the Mukaiyama reaction, stereodifferentiation leads to excellent diastereoselection and enantioselection. When silyl ketene acetal **477** was reacted with chiral aldehyde **478** in the presence of $TiCl_4$, a 75% yield of **479** and **480** was obtained as a 98:2 mixture favoring **479**.²⁸⁵



9.5.C. Chelation Control

Chelating substituents influence the stereoselectivity of enolate condensation and alkylation reactions, usually by generating a complex that is conformationally rigid. When β -hydroxy-ester **481** was treated with two equivalents of LDA, the dilithio derivative was generated. Lithium was chelated to both oxygens of the dianion, and this type of intermediate was seen in

^{285.} Shirai, F.; Nakai, T. Tetrahedron Lett. 1988, 29, 6461.

previous sections (see **422** and **456**).^{286,29} Reaction of the (*Z*) enolate (**482**) with an electrophile leads to its delivery from the less hindered face, giving the anti product **484**. In the (*E*)-enolate (**483**), chelation again leads to delivery of the electrophile from the less hindered face (away from R¹), and **484** is again the major product.^{286,29} If the hydroxyl group is blocked (protected), the chelating effect is greatly diminished or removed. Reaction of OSiR₃ derivatives of **481**, where the chelating effect is removed because there is no O–H group, with LDA/THF and an electrophile gave the opposite aldolate ratio of stereoisomers with an (*E*/*Z*) ratio of > 90:10.^{286,29} Kraus and Taschner used this analysis (structures **482** and **483**)²⁸⁶ to predict the stereoselectivity of an epoxidation reaction that gave glycidic esters (sec. 9.4.B.vi). The model was later applied to enolate alkylations and condensations, as shown.²⁹



Evans and Takacs prepared several chiral auxiliaries derived from amino alcohols such as valinol or prolinol, know known as **Evans' auxiliaries**. Prolinol amides such as **485** preferentially form the (*Z*)-enolate (**486**) over the (*E*)-enolate (**487**). Alkylation proceeds with chelation control and good diastereoselectivity (from the *si* face) to give the alkylated products **488** and **489**, favoring **488**.^{287,29} The (*Z*) enolate (**486**) is preferred over **487**, since **486** is chelated and **487** is not. Addition of the electrophile from the less hindered face of each enolate anion gives the observed products. Evans and co-workers also prepared asymmetric carbamates that showed opposite diastereoface selectivity.²⁸⁸ In both cases; small alkyl halides such as methyl iodide showed less stereoselectivity than the more sterically demanding benzyl bromide.



Diastereoselectivity is observed in reactions of carbanions derived from imines and hydrazones when those species contain a stereogenic center or a chiral auxiliary (sec. 9.4.F). Asymmetric imines can be used, and chiral oxazoline derivatives have also been prepared and used in the alkylation sequence (sec. 9.3.A). Meyers and co-workers showed that chiral oxazoline

^{286.} Kraus, G.A.; Taschner, M.J. Tetrahedron Lett. 1977, 4575.

^{287. (}a) Evans, D.A.; Takacs, J.M. Tetrahedron Lett. 1980, 21, 4233; (b) Sonnett, P.E.; Heath, R.R. J. Org. Chem. 1980, 45, 3138.

^{288.} Evans, D.A.; Ennis, M.D.; Mathre, D.J. J. Am. Chem. Soc. 1982, 104, 1737.

490 could be alkylated to give the ethyl derivative **491**.²⁸⁹ A second alkylation generated the diastereomeric product **492**, and hydrolysis provided the chiral lactone (**493**) in 58% yield and with a selectivity of 70% ee for the (*R*) enantiomer.²⁸⁹ As pointed out in Section 9.4.F.ii, hydrazone carbanions can be used for alkylation or condensation reactions. In a synthesis of (–)-callystatin A,²⁹⁰ Enders and co-worker's prepared the chiral hydrazone **495** (by reaction of the aldehyde with the hydrazone known as **SAMP** [**494**, *N*-amino-(2*S*)-(methoxymethyl) pyrrolidine)]),²⁹¹ and showed that treatment with LDA and then iodomethane gave the alkylated product. Ozonolysis cleaved the SAMP group to give methylated aldehyde **496** in 73% overall yield from **495**. The enantiomer of **494** is known as **RAMP**, *N*-amino-(2*R*)-(methoxymethyl) pyrrolidine) and both enantiomers have been applied in organic synthesis.²⁹²



9.5.D. Diastereoselectivity in Alkylidene Enolates

Enolates derived from cyclic compounds cyclohexane carboxylic acid or cyclohexanecarboxaldehyde generate enolate anions that are unique. These enolates have an exocyclic double bond that can exist as (E) and (Z) isomers. The facial and orientational bias in alkylation and condensation reactions of such enolates is influenced by the conformation of the ring it is attached to. Alkylidene cyclohexane enolates show a preference for equatorial attack, as observed in addition reactions of cyclohexanone derivatives (sec. 4.7.C,D).

The position and stereochemistry of substituents on the ring influences the selectivity. In 1,2-chiral systems such as 497, treatment with LDA leads to an equilibrating mixture of enolate anions (498A and 498B). The destabilizing Me \leftrightarrow OMe interaction in 498A is absent in 498B,

 ⁽a) Meyers, A.I.; Yamamoto, Y.; Mihelich, E.D.; Bell, R.A. J. Org. Chem. 1980, 45, 2792; (b) Hoobler, M.A.; Bergbreiter, D.Z.; Newcomb, M. J. Am. Chem. Soc. 1978, 100, 8182.

^{290.} Vicario, J.L.; Job, A.; Wolberg, M.; Müller, M.; Enders, D. Org. Lett. 2002, 4, 1023.

^{291. (}a) Enders, D.; Eichenauer, H. Chem. Ber. 1979, 112, 2933; (b) Enders, D.; Frey, P.; Kipphardt, H. Org. Synth. 1987, 65, 173.

See (a) Job, A.; Janeck, C.F.; Bettray, W.; Peters, R.; Enders, D. *Tetrahedron* 2002, 58, 2253; (b) Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M.-I.; Runsink, J.; Raabe, G. J. Org. Chem. 2005, 70, 10538.

and reaction with CH₃I proceeds from the less sterically hindered path *b* to give **499** rather than **500**.^{293,28} When R in **497** was hydrogen a 70:30 mixture of **499/500** was obtained, but when R was methyl an 80:20 mixture was obtained, favoring **499**. This result is opposite to results observed in the reduction of cyclohexanone derivatives (sec. 4.7.C). One explanation for this difference is that enolate anions such as **498A** exist as aggregates (dimers or tetramers) that increases the blockage to attack via path *a*.



A 1,3-disubstituted system is shown with ester 501, where treatment with LDA generates the equilibrating enolates 502A and 502B, favoring 502B. When the enolate precursor was the acid (R = H in 501), alkylation with iodomethane showed a slight preference for formation of **504** over **503**. Note that reaction of the acid proceeded via formation of a dianion. When R^1 was methyl (R = H in 501), however, a 52:48 mixture of 503/504 was obtained. The methyl ester of 501 (R = methyl) showed a distinct preference for 503 when R¹ was OMe, where a 78:22 mixture of 503/504 was obtained. When R^1 = methyl and R = OMe, a 90:10 mixture of 503/504 was obtained. This mixture is explained by delivery of iodomethane from path a in **502B** (equatorial attack).^{292b} Presumably, steric interactions with the OR group of the enolate moiety are minimal (or equal) in both conformations, making the conformation with the equatorial \mathbb{R}^1 group (502B) preferred. In the 1,4-disubstituted system (505), reaction with LDA generated the alkylidene enolate **506**. Alkylation with iodomethane proceeded via path b (interaction with the 1,3-diaxial hydrogens in 506 destabilized attack along path a) to give the major product (508).^{292b,294} An 84:16 mixture of 507/508 was obtained when R was either OMe or t-Bu. Addition of the electrophile favored equatorial alkylation (path b to give 507). but a mixture of 507 and 508 was obtained.



^{293. (}a) Krapcho, A.P.; Dundulis, E.A. J. Org. Chem. 1980, 45, 3236; (b) Johnson, F.; Malhotra, S.K. J. Am. Chem. Soc. 1965, 87, 5492, 5493.

^{294.} House, H.O.; Bare, T.M. J. Org. Chem. 1968, 33, 943.

$$R \leftarrow CO_2 Me \xrightarrow{1. LDA}_{2. Mel} \left[\begin{array}{c} a & OLi \\ \hline & OMe \\ b \end{array} \right] \rightarrow R \leftarrow \begin{array}{c} CO_2 Me \\ Me \\ \hline Me \\ 505 \end{array} + R \leftarrow \begin{array}{c} Me \\ CO_2 Me \\ \hline & CO_2$$

Five- and six-membered ring enolates derived from cyclopentanone and cyclohexanone derivatives have an endocyclic double bond, and reactions with an electrophile occur from the sterically less hindered face. Enolate **510** was obtained by treatment of **509** with lithium amide. Subsequent reaction with an alkyl halide led to delivery of the halide from the face opposite the alkenyl group (path *a*), to give the trans product shown (**511**) in 60% yield.²⁹⁵ Approach via path *b* would have serious steric consequences, and that transition state is destabilized. Similar effects are observed with 3-alkyl-cyclohexanone derivatives.^{296,294,295}



Delivery of an electrophile to the less hindered face of an enolate also occurs in intramolecular alkylation reactions. When **512** was treated with potassium *tert*-butoxide, a mixture of (*E*) and (*Z*) enolates (**513** and **514**, respectively) was obtained. Intramolecular displacement of bromide generated a single isomer (**515**).²⁹⁷ In this case, the electrophile can approach the enolate from only one face (the bottom or α face). Because of this conformational constraint, both (*E*) and (*Z*) enolates lead to the same product. In cyclopentanone and cyclohexanone enolates, an increase in the size of a facial blocking group increases selectivity. When that group was small, the selectivity decreased.



The preference for the lowest energy conformation of the enolate anion is seen in larger ring systems as well (sec. 1.5.B,C), leading to good selectivity in alkylation and condensation reactions. The methyl group provides only small steric encumbrance to approach of the electrophile in enolate **517** (derived from lactone **516** and LDA). The preferred mode of attack for this relatively stable conformation was from the top face (path a, pseudo-equatorial attack)

^{295.} Patterson, Jr., J.W.; Fried, J.H. J. Org. Chem. 1974, 39, 2506.

^{296.} Posner, G.H.; Sterling, J.J.; Whitten, C.E.; Lentz, C.M.; Brunelle, D.J. J. Am. Chem. Soc. 1975, 97, 107.

^{297.} House, H.O.; Sayer, T.S.B.; Yau, C.-C. J. Org. Chem. 1978, 43, 2153.
and gave the syn diastereomer (518) with >99:1 selectivity.²⁹⁸



9.6 ENAMINES

9.6.A. Preparation of Enamines

An older method is very effective in controlling the kinetic-thermodynamic product. In 1954, Stork and co-workers²⁹⁹ reported that cyclohexanone reacted with pyrrolidine to give the corresponding enamine (**519**),³⁰⁰ a term introduced by Wittig and Blumenthal.³⁰¹ An enamine is essentially a nitrogen enolate, and it can react with alkyl halides such as iodomethane to give an equilibrium mixture of the iminium salt (**510**) and the alkylated enamine (**511**).²⁹⁹ Hydrolysis with aqueous acid led to loss of pyrrolidine and formation of 2-methylcyclohexanone. A more general sequence shows the behavior of a generic enamine (**522**) reacting with a halide via the β -carbon to give α -alkyl iminium salt, via an S_N2 process. The intermediate iminium salt (**523**) can isomerize under the reaction conditions to the less substituted enamine **524** in an equilibrium process, and hydrolysis yields the corresponding α -alkyl carbonyl compound. Alkylation gives the best yields with reactive primary halides, since it is essentially an S_N2 reaction. This sequence is referred to as the **Stork enamine synthesis**.^{299,302} Enamines are usually formed by reaction of a secondary amine with a ketone, in the presence of an acid catalyst.³⁰³



^{298.} Still, W.C.; Galynker, I. Tetrahedron 1981, 37, 3981.

303. (a) Hayne, L.W. in Reference 300, pp 55-100; (b) Herr, M.E.; Heyl, F.W. J. Am. Chem. Soc. 1952, 74, 3627;
(c) Heyl, F.W.; Herr, M.E. Ibid. 1953, 75, 1918; (d) Herr, M.E.; Heyl, F.W. Ibid. 1953, 75, 5927.

^{299.} Stork, G.; Terrell, R.; Szmuszkovicz, J. J. Am. Chem. Soc. 1954, 76, 2029.

^{300.} For an older review of the chemistry of enamines see Cook, A.G. Ed., *Enamines: Synthesis Structure and Reactions*, Marcel Dekker, New York, **1969**.

^{301.} Wittig, G.; Blumenthal, H. Berichte, 1927, 60, 1085.

^{302. (}a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-90; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 628-629.

Enamines such as **522** are bidentate nucleophiles, with both nitrogen and carbon functioning as nucleophiles.³⁰⁴ Alkylation at nitrogen is a problem with reactive halides such as methyl iodide or allyl bromide, and when the groups on nitrogen are small. Nucleophilicity usually parallels that of the unsubstituted amine. In general, the kinetic nitrogen enolate (the less substituted enamine) is formed due to reduced steric hindrance.³⁰⁵ The enamine exists primarily as a planar species (**523** or **524**) in which the lone pair electrons on nitrogen are parallel with the π bond. If the steric interaction ($R \leftrightarrow R^1$) in **525** is greater than the $R \leftrightarrow Me$ interaction in **526**, there is a preference for that kinetic nitrogen enolate. When diethylamino or dimethyl-amino moieties are used, these interactions are small, and a mixture of **525** and **526** is obtained. As R and R¹ increase in size, the steric encumbrance increases, favoring **526**. Pyrrolidine, piperidine, morpholine or diethylamine are the most common amine precursors to enamines. It is noted that when aldehydes such as **527** react with secondary amines, initial reaction gives an iminium salt. Reaction with excess amine leads to aminal **528** rather than to the enamine. Treatment with a base such as sodium carbonate is required to induce elimination of the amine (pyrrolidine in this case), to give enamine **529**.³⁰⁶



9.6.B. Reactions of Enamines

As noted above, enamines behave as nitrogen enolates in their reactions with alkyl halides, generating an iminium salt (see **523**) that can isomerize to the less substituted enamine (see **524**). Although this new enamine can react with additional halide, it is present in very small

^{304.} For a review of enamine chemistry, as well as that of imines and oximes, see Adams, J.P. J. Chem. Soc. Perkin Trans. 1, 2000, 125.

 ^{305. (}a) Stork, G.; Brizzolara, A.; Landesman, H.; Szmuszkovicz, J.; Terrell, R. J. Am. Chem. Soc. 1963, 85, 207; (b) Kuehne, M. Ibid. 1959, 81, 5400; (c) Kuehne, M. Ibid. 1962, 84, 837.

^{306.} Mannich, C.; Davidsen, H. Berichte 1936, 69, 2106.

quantities in most cases, and overalkylation is not a serious side reaction. If an excess of the halide is used, however, the second alkylation can be used to advantage. A typical enamine synthesis is taken from Carpenter and Davis' work, in which ketone **530** reacted with pyrrolidine to give **531**.³⁰⁷ Reaction with ethyl bromoacetate, followed by hydrolysis gave **532**. Enamines can react with aryl halides in addition to alkyl halides, but the aryl halide must be activated by the presence of electron-withdrawing groups since this coupling reaction is formally a nucleophilic aromatic substitution (sec. 2.11.C).^{308,305c} As noted above, pyrrolidine enamines are usually too reactive at carbon for *N*-acylation to compete.



Enamines react with α , β -unsaturated compounds almost exclusively by conjugate addition to give the corresponding substituted ester, ketone or nitrile. Reaction of **519** with acrylonitrile, for example, gave a new enamine (**533**). Subsequent hydrolysis liberated the substitute ketone (**534**) in 80% overall yield from enamine **519**.^{305a,309}



With the exception of pyrrolidine enamines noted above, enamines react very efficiently with acyl halides and the product after hydrolysis is a dicarbonyl compound. The morpholine enamine of isobutryaldehyde (535) reacted with acetyl chloride to give keto-iminium salt 536. Hydrolysis gave keto aldehyde 537 in 66% yield.³¹⁰ Enamines react with acid chlorides in the



presence of a base to give a ketene, and this reacts via a thermal [2+2]-cycloaddition to give a cyclobutanone derivative (see sec. 11.10.A). Ketene formation is usually not a significant problem in acylation reactions, since the enamine is the only base in the system.³¹¹ Morpholino enamines of cyclic ketones usually give the best yield of ketone product on reaction with acyl halides. A side reaction that is sometimes important is an aldol-like reaction between enamines

^{307.} Davis, K.M.; Carpenter, B.K. J. Org. Chem. 1996, 61, 4617.

^{308.} Alt, G.H. in Reference 300, p 131.

^{309.} Williamson, W.R.N. Tetrahedron 1958, 3, 314.

^{310. (}a) Alt, G.H. in Reference 300, pp 135-136; (b) Inukai, T.; Yoshizawa, R. J. Org. Chem. 1967, 32, 404.

^{311.} Hünig, S.; Benzing, E.; Lücke, E. Berichte 1957, 90, 2833.

and aldehydes, which are both in solution,³¹² but it is not a serious problem when the enamine is derived from a ketone.

Prior to the development of kinetic control in enolate anion condensation reactions, enamines were used extensively in synthesis.^{313,314} An example is the synthesis of lupinine (**541**) using the optically active chlorocarbonate **539** and octahydroquinolizine **538**.³¹⁵ The enamine product of the initial reaction (**540**) was isolated in this case and selectively reduced to lupinine (**541**). Other reactions are possible with enamines. Cossy and Belotti reported that cyclohexene-enamines can be converted to aromatic amines.³¹⁶ In their work, cyclohexanone and pyrrolidine gave 1-pyrrolidinecyclohexene (**542**) and this was converted to 1-phenylpyrrolidine (**543**) in 83% yield by heating with palladium on carbon in the presence of nitrobenzene.



9.6.C. Asymmetric Enamine Syntheses

Asymmetric enamine derivatives generally give moderate-to-good diastereoselectivity.³¹⁷ The synthesis of lupinine (**541**) provided one example where an acid chloride substrate possessed a chiral auxiliary. An alternative approach is to prepare the enamine from a chiral amine.

$$\underbrace{ \begin{array}{c} & & \\ &$$

Yamada et al. prepared proline ester enamines such as **544**. In this case, the chiral enamine was used in a Michael addition with acrylonitrile or methyl acrylate to give **545**.³¹⁸ The yield of the ketone product was

rather poor, and the asymmetric induction (% ee) was in the range 15-59% with acrylonitrile and methyl acrylate.³¹⁸ The chiral amine precursor to the enamine was synthesized from proline derivatives. When this chiral amine was distilled extensive racemization occurred, which is a major drawback to a practical use of this procedure. In addition, some racemization

^{312. (}a) Alt, G.H. in Reference 300, pp 156-165; (b) Birkofer, L.; Kim, S.M.; Engels, H.D. Berichte 1962, 95, 1495.

^{313.} Kuehne, M.E. in Reference 300, pp 313-468

^{314.} Lansbury, P.T.; Wang, N.Y.; Rhodes, J.E. Tetrahedron Lett. 1972, 2053.

^{315.} Goldberg, S.I.; Ragade, I. J. Org. Chem. 1967, 32, 1046.

^{316.} Cossy, J.; Belotti, D. Org. Lett. 2002, 4, 2557.

Seebach, D.; Imwinkelried, R.; Weber, T. in *Modern Synthetic Methods 1986*, Scheffold, R. Ed., Springer-Verlag, Berlin, *1986*, pp 217-246.

^{318. (}a) Yamada, S.; Hiroi, K.; Achiwa, K. Tetrahedron Lett. 1969, 4233; (b) Yamada, S.; Otani, G. Ibid. 1969, 4237.

occurred during isolation of the enamine product (544). Failure to resolve these problems led to the use of crude amines and enamine products in all subsequent reactions.³¹⁹ It is possible to obtain good enantioselectivity with chiral enamines, if the chiral Me

amine precursor is carefully chosen. Whitesell and Felman found that enamine **546** reacts with alkyl halides to give chiral ketones such as **547** with good optical yields (+ MeI = 83% ee; + *n*-PrI = 93% ee; + CH₂=CHCH₂Br = 87% ee).³²⁰



The disconnections for enamine reactions are the same as those shown for enolates.

9.7. MICHAEL ADDITION AND RELATED REACTIONS

9.7.A. Michael Addition

The 1,4- (conjugate) addition^{321e} of a carbon nucleophile to an α , β -unsaturated carbonyl system is usually reversible, and referred to as **Michael addition**.³²¹ The term Michael addition is also applied to the conjugate addition of amines to unsaturated carbonyl compounds. The addition

of dimethylamine to **548** in water,³²² for example, generated **549** and illustrates the Michael addition of an amine. The rate acceleration effect observed when the reaction is done in water makes this



particular reaction less common. Enolates and carbanions are common partners in Michael additions.³²³ The anion of 1-phenyl-1,3-butanedione (**550**) generated *in situ* by reaction of the diketone with DBU, reacted with ethyl acrylate to give the Michael addition product, enolate anion **551**. Quenching the enolate anion with aqueous acid generated diketo ester **552** in 90% yield, in Taber and co-worker's synthesis of the ethyl ester of the major urinary metabolite of prostaglandin $E_{2.324}$ Conjugate addition of most enolates is often reversible, and the relative stability of the enolate starting material (**550**) versus the enolate product (**551**) will determine

 ⁽a) Bergbreiter, D.E.; Newcomb, M. in *Asymmetric Synthesis Vol. 2*, Morrison, J.D. Ed., Academic Press, New York, *1980*, pp 220; (b) Hiroi, K.; Yamada, S. *Chem. Pharm. Bull.*, *1973*, *21*, 47; (c) Otani, G.; Yamada, S. *Ibid. 1973*, *21*, 2112.

^{320.} Whitesell, J.K.; Felman, S.W. J. Org. Chem. 1977, 42, 1663.

^{321. (}a) Michael, A. J. Prakt. Chem. 1887, 35, 379; (b) Bergmann, E.D.; Gingberg, D.; Pappo, R. Org. React. 1959, 10, 179; (c) Reference 104, pp 315-316; (d) Reference 105, pp 173-174; (e) Perlmutter, P. Conjugative Addition Reactions in Organic Synthesis, Pergamon Press, Oxford, 1992; (f) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, pONR-61; (g) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 428-429.

^{322.} Naidu, B.N.; Sorenson, M.E.; Connolly, T.P.; Ueda, Y. J. Org. Chem. 2003, 68, 10098.

^{323.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd ed., Wiley-VCH, New York, 1999, p 1317.

^{324.} Taber, D.F.; Teng, D. J. Org. Chem. 2002, 67, 1607.

the position of the equilibrium. Solvent is important, and alcoholic solvents usually promote the equilibrium. Many examples of conjugate additions with Grignard reagents, organolithium reagents, or organocuprates were given in Chapter 8, and enolates also add to conjugated systems in a Michael fashion. Enantioselective Michael additions are well known,^{325a} and a lanthanide-linked BINOL complex as been used effectively for the addition of malonate anions to cyclohexenone.^{325b} One synthetic example is taken from the Takasu et al. synthesis of culmorin,³²⁶ in which treatment of **553** with LHDMS led to a double Michael addition to give **554** in 87% yield. Initial formation of enolate anion **554** allows a Michael addition to the conjugated ester to form a seven-membered ring in **555**. This newly formed ester enolate reacts with the conjugated ketone by a second Michael addition to give enolate anion **556**, which is drawn a second time to show the bicycloheptanone structure. Hydrolysis gave the final product **557**.



9.7.B. Baylis-Hillman Reaction

An interesting variation of the Michael addition has been used to prepare highly functionalized acylate derivatives. In its fundamental form, an acrylate ester reacts with an aldehyde in the presence of an amine or phosphine (such as tributylphosphine) catalyst. Presumably, Michael

addition generates an enolate anion such as **558**, which condenses with the aldehyde and then loses the phosphine or amine to give the final product **559**. This



^{325. (}a) Sibi, M.P.; Manyem, S. *Tetrahedron* 2000, 56, 8033; (b) Kim, Y.S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. J. Am. Chem. Soc. 2000, 122, 6506.

^{326.} Takasu, K.; Mizutani, S.; Noguchi, M.; Makita, K.; Ihara, M. J. Org. Chem. 2000, 65, 4112.

transformation is known as the **Baylis-Hillman reaction**³²⁷ (also known as the **Morita-Baylis-Hillman reaction**).³²⁸ Aldol condensation, induced by the amine catalyst, can be a competing side reaction. Coupling is often slow, but Leahy and Rafel found that using DABCO as the

catalyst at 0°C led to faster formation of Baylis-Hillman products, and in good yield.³²⁹ An example is the reaction of **560** with ethyl acrylate in the presence of DABCO, giving an 86% yield of **561** as a 1:1 mixture of diastereomers in the Tandano and co-worker's synthesis of (+)-tubelactomicin A.³³⁰



Chloromethyl derivatives formed from TiCl₄ and triethylamine in CH₂Cl₂ at –78°C are treated with triethylamine or DBU to give a Baylis-Hillman product.³³¹ Samarium iodide (SmI₂) mediates the Baylis-Hillman reaction.³³² Asymmetric Baylis-Hillman reactions are known.³³³ Using Oppolzer's sultam³³⁴ as an auxiliary, Leahy and co-workers³³⁵ reacted amide **562** with propanal to give an 85% yield of **563** in >99% ee.³³⁴ Treatment of **563** with camphorsulfonic acid in methanol in a second step gave an 85% yield of (+)-**564**. Another camphor-based auxiliary has also been used with success.³³⁶ A chiral acetylenic ester titanium alkoxide complex has been used to generate chiral Baylis-Hillman products,³³⁷ and the use of lanthanide triflates complexed with chiral diamine ligands derived from camphor gave Baylis-Hillman products with high enantioselectivities.³³⁸ Intramolecular Baylis-Hillman reactions have also been reported.³³⁹

- 327. (a) Ciganek, E. Org. React. 1997, 51, 201; (b) Basavaiah, D.; Rao, P.D.; Hyma, R.S. Tetrahedron 1996, 52, 8001; (c) Drewes, S.E.; Roos, G.H.P. Tetrahedron 1988, 44, 4653; (d) Shi, M.; Li, C.-Q.; Jiang, J.-K. Tetrahedron 2003, 59, 1181; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-7; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 74-75.
- 328. (a) Morita, K.; Suzuki, Z.; Hirose, H. Bull. Chem. Soc. Jpn. 1968, 41, 2815. (b) Baylis, A.B.; Hillman, M E.D. German Patent 2155113, 1972 (Chem. Abstr. 1972, 77: 34174q). For a recent review, see (c) Basavaiah, D.; Rao, A.J.: Satyanarayana, T. Chem. Rev. 2003, 103, 811.
- 329. Rafel, S.; Leahy, J.W. J. Org. Chem. 1997, 62, 1521.
- Motozaki, T.; Sawamura, K.; Suzuki, A.; Yoshida, K.; Ueki, T.; Ohara, A.; Munakata, R.; Takao, K.-i.; Tadano, K.-i. Org. Lett. 2005, 7, 2265.
- 331. Shi, M.; Jiang, J.-K.; Feng, Y.-S. Org. Lett. 2000, 2, 2397.
- 332. Youn, S.W.; Park, H.S.; Kim, Y.H. Chem. Commun. 2000, 2005.
- 333. Langer, P. Angew. Chem. Int. Ed. 2000, 39, 3049.
- (a) Oppolzer, W. Pure Appl. Chem. 1990, 62, 1241; b) Kim, B.H.; Curran, D.P. Tetrahedron 1993, 49, 293;
 (c) Oppolzer, W. Tetrahedron 1987, 43, 1969; (d) Oppolzer, W. Pure Appl. Chem. 1988, 60, 39.
- 335. Brezinski, L.J.; Rafel, S.; Leahy, J.W. J. Am. Chem. Soc. 1997, 119, 4317.
- 336. Yang, K.-S.; Chen, K. Org. Lett. 2000, 2, 729.
- 337. Suzuki, D.; Urabe, H.; Sato, F. Angew. Chem. Int. Ed. 2000, 39, 3290.
- 338. Yang, K.-S.; Lee, W.-D.; Pan, J.-F.; Chen, K. J. Org. Chem. 2003, 68, 915.
- 339. Keck, G.E.; Welch, D.S. Org. Lett. 2002, 4, 3687. Also see Krishna, P.R.; Kannan, V.; Sharma, G.V.M. J. Org. Chem. 2004, 69, 6467.

$$\begin{array}{c} & & & \\ & & & \\ &$$

9.7.C. Robinson Annulation

A major synthetic challenge in the 1930s through the 1950s was construction of various steroid molecules. One important route that emerged from this effort was the use of a Michael addition protocol to produce a bicyclic ketone. This sequence soon came to be known as the **Robinson annulation**.^{340,321d} The reaction can be illustrated by treatment of 3-pentanone with sodium ethoxide (equilibrating conditions) in the presence of MVK. Other bases have been used, including lanthanoid triisopropoxides that behave as catalysts in this reaction.³⁴¹ The initial product is a cyclic alkoxy ketone (**565**), which gives alcohol **566** upon hydrolysis. This alcohol usually loses water with heating to give enone **567** as the final Robinson annulation product.



The reaction conditions favor formation of a thermodynamic enolate, although this is irrelevant with 3-pentanone. Conversion of 3-pentanone to its enolate (127) was followed by Michael addition to MVK to give a new enolate product (568). This enolate could react with the carbonyl at C6 to give a four-membered ring (path a), but as discussed in Sections 6.6.A,B, the energy requirements for this reaction are relatively high and the process is energetically unfavorable. Under the equilibrium conditions of the reaction, a small portion of kinetic enolate 569 can be formed. An intramolecular aldol condensation at C6 is possible (path b) that generates a six-membered ring (565), and this is energetically more favorable than forming a four-membered ring from 568. When a cyclic ketone such as cyclohexanone reacts with MVK, Robinson annulation generates a bicyclic ketone.^{340b-e}

^{340. (}a) Annulation is the act or process of forming a ring; the formation of rings or ring-shaped parts. Annelation is an alternative but less desirable term, which means to anneal one ring onto another. The term annelation refers to the phenomenon whereby some rings in fused systems give up part of their aromaticity to adjacent rings, as on p. 61 in Smith, M.B.; March, J. *March's Advanced Organic Chemistry, 6th ed.*; Wiley, New York, *2007*; (b) DuFeu, E.C.; McQuillin, F.J.; Robinson, R. *J. Chem. Soc. 1937*, 53; (c) Balasubramanian, K.; John, J.P.; Swamnathan, S. *Synthesis 1974*, 51; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, *2006*, p ONR-80; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, *2005*, pp. 556-557.

^{341.} Okano, T.; Satou, Y.; Tamura, M.; Kiji, J. Bull. Chem. Soc. Jpn. 1997, 70, 1879.



A synthetic example is taken from a synthesis of ouabain by Jung and Piizzi,³⁴² in which β -keto ester **570** reacted with methyl vinyl ketone and ethanolic potassium *tert*-butoxide to give **571** in good yield. There are many variations of the Robinson annulation that can be used to prepare synthetically useful products,^{343,344} including some using a conjugated ketone surrogate known as a **Mannich base** such as **572**. Under the basic conditions of the Robinson annulation, the β -amino ketone eliminates diethylamine to form the conjugated ketone *in situ*, which may avoid the deleterious side reactions caused by the equilibrium conditions. A Mannich base is produced by a **Mannich reaction**,³⁴⁵ where dimethylamine, for example, reacts with formaldehyde and acetone to give **572**.^{345a,346} Acid-catalyzed Robinson annulation reactions are also known. An example is the conversion of **573** to **574** in good yield.³⁴⁷



The Robinson Annulation disconnection is



^{342.} Jung, M.E.; Piizzi, G. Org. Lett. 2003, 5, 137.

- 344. Hackett, S.; Livinghouse, T. J. Org. Chem. 1986, 51, 1629.
- 345. (a) Mannich, C.; Krösche, W. Arch. Pharm. 1912, 250, 647; (b) Blicke, F.F. Org. React. 1942, 1, 303; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-57; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 408-409.
- 346. For a synthetic example using a Manich reaction for saframycin alkaloids, see Zhou, B.; Guo, J.; Danishefsky, S.J. *Tetrahedron Lett.* **2000**, *41*, 2043.
- 347. Busch-Petersen, J.; Corey, E.J. Tetrahedron Lett. 2000, 41, 6941.

^{343.} Scott, W.L.; Evans, D.A. J. Am. Chem. Soc. 1972, 94, 4779.

The reversible nature of the initial Michael addition is a problem with the Robinson annulation. A solution is to use a conjugated system that is particularly prone to Michael addition and forms the product, essentially irreversibly. α -Silyl vinyl ketones have been shown to be powerful Michael acceptors.³⁴⁸ The lithium enolate of cyclohexanone reacted with conjugated ketone **575** to produce the Michael product, **576**.^{348a} In this case, the initially formed Michael adduct was stabilized by the presence of the silyl group at the α -position, driving the reaction toward the product. Hydrolysis produced **577**, which was converted to the Robinson product (**578**) in 80% overall yield by treatment with NaOMe/MeOH under the requisite thermo-dynamic conditions.^{348a} When compared to this sequential process, normal treatment of cyclohexanone enolate with MVK under Robinson conditions, which gave adduct **578** in < 5% yield.



9.7.D. Selectivity in the Robinson Annulation

Many modifications of the fundamental Robinson annulation sequence have appeared over the years, one of which uses silvl derivatives such as **575**. An important modification uses chiral precursors or chiral additives to give asymmetric induction either during the Michael addition, during the aldol cyclization or in both reactions. Excellent asymmetric induction has been obtained by using an asymmetric base such as (S)-(–)-proline (shown in the reaction) to generate

the enolate. Hajos and Parrish obtained bicyclic ketone **580** (**Hajos diketone**) by treating **579** with MVK and proline. The Robinson product (**580**) was isolated with an optical purity of 93.4%.³⁴⁹ Proline acts as a



catalyst in an asymmetric Robinson annulation.³⁵⁰ Similarly, Wynberg and Helder showed that addition of asymmetric catalysts such as *Cinchona* alkaloids gave optical yields of 5-25% ee for Michael additions of cyclohexanone derivatives,³⁵¹ but up to 71% ee in some cases.³⁵² Langstrom and Bergson first employed asymmetric catalysts in the Michael addition.³⁵³ An antibody-catalyzed enantioselective Robinson annulation has also been reported.³⁵⁴

^{348. (}a) Stork, G.; Ganem, B. J. Am. Chem. Soc. 1973, 95, 6152; (b) Stork, G.; Singh, J. Ibid. 1974, 96, 6181.

^{349.} Hajos, Z.G.; Parrish, D.R. J. Org. Chem. 1974, 39, 1612, 1615

^{350.} Bui, T.; Barbas III, C.F. Tetrahedron Lett. 2000, 41, 6951.

^{351.} Hermann, K.; Wynberg, H. J. Org. Chem. 1979, 44, 2238.

^{352.} Wynberg, H.; Helder, R. Tetrahedron Lett. 1975, 4057.

^{353.} Langstrom, B.; Bergson, G. Acta Chem. Scand. 1973, 27, 3118.

^{354.} Zhong, G.; Hoffmann, T.; Lerner, R.A.; Danishefsky, S.; Barbas III, C.F. J. Am. Chem. Soc. 1997, 119, 8131.

Solvent influences the stereochemistry of the Robinson annulation.³⁵⁵ The condensation of methylcyclohexanone and **581** with sodium hydride in dioxane led to >95% of **582** with syn relationship for the methyl groups. Similar reaction in DMSO, however, led to >95% of **583** with had an anti relationship for those methyl groups. The change in stereochemistry was explained by a hydrogen transfer, that is facile in the highly polar DMSO but not in dioxane.³⁵⁰ In general, polar protic solvents tend to give the trans product whereas less polar aprotic solvents favor the cis product.



The metal also plays a role. The presence of a highly covalent O–Li bond favors the trans product, but a more ionic O–Na or O–K bond in alcoholic solvents favors the cis.³⁵⁵ The lithium species is less bulky, due to poorer solvation in the aprotic solvent. The protic solvent hydrogen bonds extensively with the ionic sodium species, leading to a large increase in the relative size of the alkoxide moiety. This bulky group influences the geometry of the intermediate and leads to an increase in the cis product.³⁵⁵

9.8. ENOLATE REACTIONS OF α -HALO CARBONYL DERIVATIVES

9.8.A. α -Halogenation

Several reactions formally involve enolates, but the course of the reaction is altered by the presence of reactive functionality. The **Darzens' glycidic ester synthesis** discussed in Section 9.4.B.vi is one example. Another involves the formation of α -halogenated ketones. Treatment of a ketone with X₂ or NXS (X = Cl, Br, I) usually gives the α -halo ketone, as in the conversion of cyclopentanone to 2-bromocyclopentanone.³⁵⁶ When there is the possibility of forming kinetic and thermodynamic products, the thermodynamic product usually predominates. In the synthesis of this α -bromoketone, KClO₃ oxidized the HBr byproduct back to Br₂. A serious problem in the halogenation is further reaction of the product with the halogen to give an α , α -dihalo accuracy.

dihalo compound. The presence of the first halogen promotes further enolization and polyhalogenation is often a serious problem. Halogenation of silyl enol ethers



^{355. (}a) Marshall, J.A.; Warne, Jr., T.M. J. Org. Chem. 1971, 36, 178; (b) Scanio, C.J.V.; Starrett, R.M. J. Am. Chem. Soc. 1971, 93, 1539.

 ⁽a) Reed, Jr., S.F. J. Org. Chem. 1965, 30, 2195; (b) Rappe, C.; Kumar, R. Arkiv. Kemi. 1965, 23, 475 [Chem. Abstr. 63: 5521c 1965]; (c) Zbiral, E.; Rasberger, M. Tetrahedron 1969, 25, 1871; (d) Wyman, D.P.; Kaufman, P.R. J. Org. Chem. 1964, 29, 1956.

gives a good yield of monohaloketone.³⁵⁷ Cupric (Cu²⁺) salts such as CuCl₂ and CuBr₂ are often added to convert a ketone to α -chloro or α -bromo ketones.³⁵⁸ The presence of the halogen modifies the bond polarity of the molecule so that displacement of halogen by nucleophiles is faster than acyl addition to the carbonyl. The reaction of 2-bromocyclopentanone with phenylmagnesium bromide gave 2-phenylcyclopentanone,³⁵⁹ for example. This variation of the Grignard reaction is an excellent route to α -aryl ketones³⁵³ (sec. 8.4.B.ii).

This leads to the interesting disconnection:

$$\bigcup_{Ar(R)}^{O} \bigoplus_{Ar(R)} \bigcup_{Ar(R)} + Ar - X (R - X) \text{ where } Ar = aryl$$

Polyhalogenation can be a severe side reaction in the formation of α -halo ketones, but can be used to synthetic advantage in the **haloform reaction** (this has been called the **Lieben iodoform reaction**).³⁶⁰ Reaction of 2-butanone with sodium hydroxide gave the enolate, and in the presence of bromine the enolate displaced bromide from Br–Br to form **584**. Incorporation of the bromine made the α -hydrogen more acidic, and a second bromination occurred to give **585**, followed by a third bromination to give **586**. Nucleophilic acyl addition of hydroxide to all carbonyl derivatives (e.g., 2-butanone, **584** and **585**) was reversible up to this point.



The Br_3C^- group is a good leaving group, however, so nucleophilic attack at the carbonyl leads to cleavage of the O=C-CBr₃ bond (via **587**) to produce butanoic acid and Br_3C^- . This carbanion rapidly deprotonated butanoic acid to produce the two final products, butanoic acid and a haloform (bromoform, CHBr₃). This sequence is a synthetic method for oxidative cleavage of a methyl group attached to the carbonyl, complementing the known cleavage of carbonyls by Cr(VI) (sec. 3.8.C). This reaction also cleaves the H₃C-C bond of methyl

^{357. (}a) Reuss, R.H.; Hassner, A. J. Org. Chem. 1974, 39, 1785; (b) Blanco, L.; Amice, P.; Conia, J.M. Synthesis 1976, 194, 196.

^{358.} Smith, M.B.; March, J. *March's Advanced Organic Chemistry, 6th ed.*, Wiley-Interscience, Hoboken, New Jersey, *2007*, pp 776-780.

^{359.} Ando, T. Yuki Gosei Kagaku Kyokaishi 1959, 17, 777 [Chem. Abstr. 54: 4492b 1960].

 ⁽a) Fuson, R.C.; Bull, B.A. Chem. Rev. 1934, 15, 275; (b) Seelye, R.N.; Turney, T.A.; J. Chem. Educ. 1959, 36, 572; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-56; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 392-393.

carbinols [RCH(OH)Me] to give the corresponding acid and iodoform. When iodine is used rather than bromine, the cleavage of methyl ketones or methyl carbinols is referred to as the **iodoform reaction**. The iodoform reaction constitutes a classical test for the presence of a methyl ketone moiety or a methyl carbinol moiety in an unknown molecule.

The haloform disconnection is



9.8.B. The Reformatsky Reaction

Another enolate-like reaction is the **Reformatsky reaction**,³⁶¹ which employs a nucleophilic organozinc intermediate, generated from an α -halo carbonyl and zinc metal. This condensation reaction is widely used in synthesis.³⁶² The organozinc reagent, in this case derived from ethyl 2-bromopropanoate (see **588**), attacks the carbonyl of an aldehyde or ketone (such as acetophenone) to give **589**. Hydrolysis gives the condensation product, β -hydroxyester **590**.



Preparation of the organozinc complex in the Reformatsky reaction can be a problem, and it often requires special preparation of the zinc (activated zinc). Activated zinc has been prepared by various procedures.³⁶³ The use of ultrasound techniques produces a finely dispersed zinc that also facilitates the Reformatsky reaction.³⁶⁴ As noted above, hydrolysis gives the hydroxy ester (**590**) to complete this two-carbon chain extension process. The organozinc reagent is generally less reactive than a Grignard or organolithium reagent, and condensation reactions proceed well with aldehydes and ketones but are sluggish with esters. A synthetic example is taken from a synthesis of rhinocerotinoic acid by Rivett and co-workers,³⁶⁵ in which ketone **591** was treated with Zn and ethyl bromoacetate to give a 93% yield of **592** as a 1:1 mixture of epimers. A SmI₃ reaction has been reported that gives the Reformatsky product (see sec. 9.8.B)

- 362. Ocampo, R.; Dolbier Jr., W.R. Tetrahedron 2004, 60, 9325.
- 363. (a) Rieke, R.D.; Li, P.T.-J.; Burns, T.P.; Uhm, S.T. J. Org. Chem. 1981, 46, 4323; (b) Rieke, R.D.; Uhm, S.J. Synthesis 1975, 452.
- 364. Han, B.H.; Boudjouk, P. J. Org. Chem. 1982, 47, 5030.
- 365. Gray, C.A.; Davies-Coleman, M.T.; Rivett, D.E.Q. Tetrahedron 2003, 59, 165.

^{361. (}a) Reformatsky, S. *Berichte* 1887, 20, 1210; (b) Diaper, D.G.M.; Kuksis A. *Chem. Rev.* 1959, 59, 89; (c) Rathke, M.W. *Org. React.* 1975, 22, 423; (d) Reference 104, pp 370-371; (e) Reference 105, pp 200-202; (f) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-78; (g) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 544-545.

with high diastereoselectivity in aqueous media.³⁶⁶ Vedejs and Ahmad used an intramolecular version of this reaction aimed at the cytochalasin ring system.³⁶⁷ In this reaction, **593**, was cyclized to give **594** as a 1:1 mixture of epimeric alcohols. The use of highly reactive **Rieke zinc**³⁶⁸ led to a 75% yield of **594**. When samarium iodide (SmI₂) in trifluoroacetic acid was used for the cyclization,³⁶⁹ a 46% yield of **592** was obtained as one diastereomeric alcohol.



The Reformatsky disconnection is

$$R^{2} \xrightarrow[OH]{R^{3}} CO_{2}R \ \Box \ A^{1} \xrightarrow[R^{2}]{R^{2}} + \ A^{3} \xrightarrow[CO_{2}R]{R^{3}}$$

The selectivity of the Reformatsky reaction is apparent in Table 9.13,^{370,371} taken from Heathcock's work, which shows the syn/anti selectivity for the hydroxy ester products (anti product **595** and syn product **596**) resulting from reaction of α -haloesters with ketones and aldehydes.³⁷¹ Aldehydes generally show poorer selectivity than do ketones for formation of the anti product, **595**. The bromozinc aldolate products from ketones were shown to equilibrate under reaction conditions, but those from aldehydes did not. In general, increasing the size of R² in the α -halo-carbonyl derivative led to greater anti selectivity.

^{366.} Hayakawa, R.; Shimizu, M. Chem. Lett. 1999, 591.

^{367.} Vedejs, E.; Ahmad, S. Tetrahedron Lett. 1988, 29, 2291.

^{368.} Arnold, R.T.; Kulenovic, S.T. Synth. Commun. 1977, 7, 223.

^{369.} Tabuchi, T.; Kawamura, K.; Inanaga, J.; Yamaguchi, M. Tetrahedron Lett. 1986, 27, 3889.

^{370.} Reference 244, pp 144-152.

^{371. (}a) Reference 244, p 146; (b) Canceill, J.; Basselier, J.J.; Jacques, J. Bull. Soc. Chim. Fr. 1967, 1024; (c) Canceill, J.; Jacques, J. Ibid. 1970, 2180.

$\begin{array}{c} O \\ Ph \end{array} + \begin{array}{c} R^{2} \\ R^{1} \end{array} + \begin{array}{c} CO_{2}Me \\ Br \end{array} \xrightarrow{Zn^{\circ}, \text{ benzene}} \\ reflux \end{array} \xrightarrow{R^{1} OH \\ Ph \end{array} \xrightarrow{E} \begin{array}{c} CO_{2}Me \\ R^{2} \end{array} + \begin{array}{c} R^{1} OH \\ Ph \end{array} \xrightarrow{E} \begin{array}{c} CO_{2}Me \\ R^{2} \end{array} + \begin{array}{c} R^{1} OH \\ Ph \end{array} \xrightarrow{CO_{2}Me} \begin{array}{c} R^{2} \\ R^{2} \end{array} 595 $					
<u>R</u> 1	<u>R²</u>	<u>593 : 594</u>	<u>R</u> 1	<u>R</u> ²	<u>593 : 594</u>
Н	Me	37:63	Н	Ph	76:24
Н	Et	46 : 54	Me	Me	67:33
Н	<i>i</i> -Pr	53:47	Me	Et	70:30
Н	c-C ₆ H ₁₁	50:50	Me	<i>i</i> -Pr	83:17
Н	<i>t</i> -Bu	69:31			

Table 9.13. syn/anti Selectivity in the Reformatsky Reaction

In more recent work, germanium catalysts such as GeCl₄ gave a highly diastereoselective Reformatsky reaction favoring the syn diastereomer.³⁷² Another syn selective reaction was reported using TiCl₂ and Cu.³⁷³ Enantioselective Reformatsky reactions have also used chiral amino alcohols as additives.³⁷⁴

9.8.C. The Favorskii Rearrangement

There is a classical reaction of enolate anions derived from α -halo ketones that involves a rearrangement. In the **Favorskii rearrangement**,³⁷⁵ also called the **Wallach degradation**, a α -chloroketone such as 2-chlorocyclohexanone is treated with NaOH under thermodynamic conditions to form the enolate anion **597**. Intramolecular displacement of chlorine leads to **598**, which is attacked by hydroxide to give the acyl addition product, **599**. Cleavage of the adjacent C–C bond leads to enolate **600**, which is protonated by the adjacent carboxylic acid to give carboxylate **601**. Hydrolysis gives the final product, cyclopentanecarboxylic acid. This reaction can be useful synthetically, as in Ley and co-worker's synthesis of trilobolide.³⁷⁶ Treatment of **602** with sodium methoxide gave a 95%% yield of the Favorskii rearrangement product (**603**), obtained as the methyl ester since the reaction was done in methanol.

^{372.} Kagoshima, H.; Hashimoto, Y.; Oguro, D.; Saigo, K. J. Org. Chem. 1998, 63, 691.

^{373.} Mukaiyama, T.; Kagayama, A.; Igarashi, K.; Shiina, I. Chem. Lett. 1999, 1157.

 ^{374. (}a) Andrés, J.M.; Martín, Y.; Pedrosa, R.; Pérez-Encabo, A. *Tetrahedron* 1997, 53, 3787; (b) Mi, A.; Wang, Z.; Zhang, J.; Jiang, Y. Synth. Commun. 1997, 27, 1469.

^{375. (}a) Favorskii, A.E. J. Prakt. Chem. 1913, 88, 658; (b) Wallach, O. Annalen, 1918, 414, 296; (c) Kende, A.S. Org. React. 1960, 11, 261; (d) Turro, N.J. Acc. Chem. Res. 1969, 2, 25; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-30; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 238-239.

^{376. (}a) Oliver, S.F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M.D.; Ley, S.V. Angew. Chem. 2003, 42, 5996; (b) Also see Lee, E.; Yoon, C.H. J. Chem. Soc. Chem. Commun. 1994, 479.



9.9. CONCLUSION

In conclusion, the reaction of enolates with alkyl halides and carbonyl compounds provides one of the most powerful and useful of all carbon-carbon bond-forming processes. Not only are a variety of synthetic products available, but the reaction can be made to proceed with excellent diastereoselectivity. In conjunction with the reactions of carbanions, nucleophilic methods constitute the largest single type of methodology for making new carbon-carbon bonds.

HOMEWORK

1. Predict the major product of this reaction, and explain the stereochemistry.



2. Explain formation of the product shown given the reaction conditions.



3. Give a mechanistic rationale for the following reaction.



4. In the following sequence, pulegone is transformed into 2,3-dimethylcyclohexanone. Explain this transformation.



5. For the reactions shown, draw the syn and anti products. Explain why there is a difference in selectivity and why the anti product predominates with PhCHO but there is essentially a 1:1 mixture with cyclohexanone.

- 6. For the reaction of 3-pentanone and lithium diisopropylamide (-78°C, THF):
 - (a) Draw both (E) and (Z) enolates.
 - (b) Give the major product of the (Z) enolate when PhCHO approaches from the *re* face;

from the si face.

Show the Zimmerman-Traxler model for both approaches.

(c) Give the major product when the (*E*) enolate reacts with *A*, assuming *A* is chiral and nonracemic.



- (d) Give the major product when the (Z) enolate reacts with chiral, non-racemic A.
- 7. Predict the major product (A or B) for each reaction. Discuss formation of each product and why each reaction might follow a different pathway.



8. Enolate formation is an acid-base equilibrium process. For reactions A and B, discuss the relative acidity of all hydrogens in 3-methyl-2-butanone. Discuss the role of solvent, base, temperature and reaction time for reactions A and B.

B
$$\leftarrow$$
 LiN(*i*-Pr)₂, THF
 -78° C, 30 min \rightarrow Me $\xrightarrow{\text{NaOEt, EtOH, 20 h}}$ **A**

Write the acid-base equations for both A and B using the standard reaction shown.

acid + base
$$\xrightarrow{K_a}$$
 conjugate acid + conjugate base

9. Explain the following transformation.



10. In each of the following reactions, predict the major diastereomer and show the Zimmerman-Traxler transition state:

(a) Ph
$$CO_2Me$$
 $\frac{1. \text{ LDA, THF, } -78^{\circ}\text{C}}{2. i\text{-PrCHO} 3. \text{H}_3\text{O}^+}$ (b) Ph CO_2H $\frac{1. n\text{-BuLi } 2. \text{LiN}(i\text{-P})_2}{3. \text{PhCHO} 4. \text{H}_2\text{O}}$



11. Use models to predict the major diastereomer formed during this methylation reaction.



12. Provide a mechanism for the following transformation.



13. Provide a mechanistic rationale for the following transformation.



14. For each of the following, give all products. What is the strategic purpose of the first condensation with benzaldehyde? Compare and contrast routes A and B:



15. Show a full synthetic sequence, with all intermediate products and reagents, for conversion of 1-methyl-1-cyclohexene into each of the molecules shown.



16. In each case, give the major product, with correct stereochemistry where appropriate.





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17. In each case, provide a suitable synthesis. Provide all reagents and show all intermediate products.





18. For each of the following, choose a commercially available starting material (give the commercial source and the price) of six carbons or less. Convert that starting material into the target shown, showing all intermediate products and all reagents. Give the commercial price of all reagents used. Show your retrosynthetic analysis:



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Synthetic Strategies

10.1. INTRODUCTION

chapter

Throughout this book, functional group transforms for each new reaction were shown at the end of the discussion. In addition, disconnections for carbon-carbon bond-forming reactions have also been given. These transforms and disconnections form the basis of the modern approach to total synthesis. Complex molecules may require alternative strategies for their total synthesis rather than the simple ones presented earlier in this book.

The logic and planning behind Corey's many syntheses spanning over 30 years were summarized in a monograph.^{1a} That monograph detailed several strategic approaches to total syntheses where those principles were applied. Nicolaou and co-authors have also published collections of total syntheses.^{1b,c} The science of total synthesis dates to the nineteenth century, and Corey cited many examples that illustrate its history. In 1904 Perkin synthesized terpineol (1),² in



part to ascertain the actual structure of this natural product. In the synthesis of tropinone (2) by Robinson in 1917,³ he envisioned that an "imaginary hydrolysis of the substance (tropinone) may be resolved into succinaldehyde, methylamine and acetone."^{4b} In this analysis we can apply



modern strategy terminology to saw that he is disconnecting **2** into simple disconnect fragments. The synthesis of equilenin (**3**) by Bachmann et al. in 1939^4 was the first multi-step synthesis of a steroid precursor to estrone. Fischer and Kirstahler synthesized hemin (**4**)⁵

- (a) Corey, E.J.; Cheng, X.-M. *The Logic of Chemical Synthesis*, Wiley, New York, *1989*; (b) Nicolaou, K.C.; Snyder, S.A. *Classics in Total Synthesis II : More Targets, Strategies, Methods, Wiley, New York, 2003*; (c) Nicolaou, K.C.; Sorenson, E.J. *Classics in Total Synthesis, 1996*, VCH, Weinheim.
- 2. Perkin, Jr., W.H. J. Chem. Soc. 1904, 85, 654.
- (a) Robinson, R. J. Chem. Soc. 1917, 111, 762; (b) Fleming, I. Selected Organic Syntheses, Wiley, London, 1973, p 18.
- 4. Bachmann, W.E.; Cole, W.; Wilds, A.L. J. Am. Chem. Soc. 1939, 61, 974.
- 5. (a) Fischer, H.; Kirstahler, A. Annalen 1928, 466, 178; (b) Fischer, H.; Zeile, K. Ibid. 1929, 468, 98.

and recognized that four similar pyrrole units composed the structure, requiring the synthesis of each fragment prior to assembling **4**.



OH With Woodward, synthesis assumed a sophistication previously unknown,⁶ and targets such as quinine (5, with von E. Doering),⁷ cortisone (6),⁸ strychnine (7)⁹ or reserpine (8)¹⁰ were synthesized (along with many other molecules). Over these years, the structural and stereochemical

features of the targets increased in complexity. As more complex structures were targeted, the newly acquired ability to control stereochemical features and stereogenic centers led to greater synthetic achievements. Corey formalized the terminology



for this approach to synthesis, making it an understandable process. This approach is called **retrosynthesis**, and it allows one to dissect a molecule and arrive at relatively simple starting materials in what is now called the **disconnection (or synthon) approach**.¹¹ Most chemists now use the disconnection approach when they undertake a synthetic problem, but there are other strategies that can be applied to planning a synthesis. Corey included several strategies for synthesis in a computer program called LHASA (sec. 10.4.B), with the goals of assisting chemists in synthetic planning and actually suggesting syntheses for complex molecules. This approach to synthesis will be presented later in this chapter, as will other techniques for assembling a retrosynthetic plan.

10.2. TARGET SELECTION

10.2.A. What Is the Rationale for Total Synthesis?

The choice of a target is obviously the point of departure for a synthesis. The synthesis of an

9. Woodward, R.B.; Cava, M.P.; Ollis, W.D.; Hunger, A.; Daeniker, H.U.; Schenker, K. Tetrahedron 1963, 19, 247.

^{6.} Woodward, R.B. in *Perspectives in Organic Chemistry*, Todd, A.R. (Ed., Interscience, New York, **1956**, pp 159-184.

^{7.} Woodward, R.B.; Doering, W.E. J. Am. Chem. Soc. 1945, 67, 860.

^{8. (}a) Woodward, R.B.; Sondheimer, F.; Taub, D.; Heusler, K.; McLamore, W.M. J. Am. Chem. Soc. 1952, 74, 4223; (b) Woodward, R.B.; Sondheimer, F.; Taub, D. Ibid. 1951, 73, 4057, 3547.

^{10.} Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. Tetrahedron 1958, 2, 1.

^{11.} Reference 1, pp 81-91.

organic molecule usually begins with two questions: (I) why was this molecule chosen as a target? and (2) where do I begin? The answer to (I) often lies in the needs and interests of the synthetic chemist. It may be a challenging stereochemical problem or functional group combination. A molecule may possess unique chemical or biological properties. The answer to (2) is the basis for this chapter.

Many reasons are cited for a synthesis, and the challenging problems encountered in a total synthesis provide many opportunities to find new reactions, processes or strategies that may be of value to other organic chemists. Corey and Wipke¹² stated a few of the useful applications that may be found in a retrosynthetic analysis-synthesis problem. Many of these may be useful in solving problems for another target, or in applications to a completely different area of organic chemistry.

"As a synthetic tree (secs. 10.3, 10.4) is developed, findings may emerge which suggest new relationships or simplifications that can lead to even more effective analysis of the original target structure. In this sense, it can be said that imbedded in each problem is a learning opportunity, which if seized can lead to extraordinarily simple or elegant situations. Learning opportunities are equally great in the subsequent stages of synthetic work which involve (i) the selection of specific chemical reactions for transforming one synthetic intermediate to the next in the sequence, (ii) the selection of specific reagents, (iii) the design of experiments, and (iv) experimental execution and analysis. During these stages observations, discoveries, inventions, or theorems of great importance may result."¹²

A similar fundamental basis for total synthesis was described by Deslongchamps.¹³

"Nowadays, for synthetic chemists interested in making fundamental contributions to their field of research, the choice of a given target is not which should be considered as the most important decision; the choice of a specific target is simply an excuse to put in practice a new strategy or to demonstrate the value of, either a new reaction, or a new set of reaction conditions. Also, when one chooses a very difficult target with these principles in mind, it creates a must to innovate in order to succeed. In other words, since the researcher has put himself or herself in a situation that organic chemists have not faced before, the chances of discovering something new and original are then quite high."¹³

"The preceding suggests that what is most important is not the choice of a given target, but how the goal is going to be achieved. In other words, it is the chemistry that one discovers along the way that is the important parameter, not the fact that one succeeds in the synthesis of a given compound, natural or non-natural. Indeed, when peers eventually have to evaluate one's work, either on a short-term or even more so on a long-term basis, it is only the value of the chemistry that will be deemed important. The fact that a total synthesis is reported for the

^{12.} Corey, E.J.; Wipke, W.T. Science 1969, 166, 178.

^{13.} Deslongchamps, P. Aldrichimica Acta 1984, 17, 59.

first time or that the compound has important biological properties or is of theoretical interest is of secondary importance from a chemical point of view".¹³

It is often true that synthesis of a particular target is of paramount importance to an individual or organization. The criterion for that importance is always obvious to the researcher(s). To one beginning a study of organic reactions and synthesis, however, it may be of value to examine several commonly quoted criteria for synthesis. These criteria, along with Corey's and also Deslongchamps' evaluations, provide a reasonable answer to question (1). The disconnection approach in its several forms will be used to address question (2).

In addition to the eight molecules shown in the introduction, six molecules are shown as examples of the wide variety of organic molecules that have been synthetic targets. Dysidiolide (9), isolated from the marine sponge *Dysidea etheria* de Laubenfels is a natural inhibitor of a protein phosphatase called csc25A, which is involved in a signaling system for cell division and a potential target for anticancer therapy.¹⁴ Not all targets come from nature. Viagra (sildenafil, 10)¹⁵ was developed by Pfizer Inc. to treat impotence, and Merck Inc. developed indinavir (11)¹⁶ as a HIV-1 protease inhibitor. Epothilone (12) is a compound with the same mechanism of action as the important anticancer drug taxol, but has a less complex structure that makes it easier to prepare.¹⁷ Pancratistatin (13) has been an important target for organic synthesis due to

 ⁽a) Gunaskera, G.P.; McCarthy, P.J.; Kelly-Borges, M.; Lobkovsky, E.; Clardy, J. J. Am. Chem. Soc. 1996, 118, 8759; (b) Blanchard, J.L.; Epstein, D.M.; Boisclair, M.D.; Rudolph, J.; Pal, K. Bioorg. Med. Chem. Lett. 1999, 9, 2537.

 ⁽a) Bell, A.S.; Brown, D.T.; Nicholas, K. *Eur. Pat. Appl. EP 463 756* [*Chem. Abstr.* 1992, 116:P255626q].
 For biological activity, see (b) Boolell, M.; Gepi-Attee, S.; Gingell, J.C.; Allen, M.J. *Br. J. Urol* 1996, 78, 257; (c) Terrett, N.K.; Bell, A.S.; Brown, D.; Ellis, P. *Bioorg. Med. Chem. Lett.* 1996, 6, 1819.

 ⁽a) Vacca, J.P.; Holloway, M.K.; Dorsey, B.D.; Hungate, R.W.; Guare, J.P. Eur. Pat. Appl. 541,168 [*Chem. Abstr. 120*: 54552w 1994]; (b) Vacca, J.P.; Dorsey, B.D.; Guare, J.P.; Holloway, M.K.; Hungate, R.W.; Levin, R.B. US Patent 5,413,999 [*Chem. Abstr. 123*: 47889v 1995]; (c) Dorsey, B.D.; Levin, R.B.; McDaniel, S.L.; Vacca, J.P.; Guare, J.P.; Darke, P.L.; Zugay, J.; Emini, E.A.; Schleif, W.A.; Quintero, J.C.; Lin, J.H.; Chen, I.-W.; Holloway, M.K.; Fitzgerald, P.M.D.; Axel, M.G.; Ostovic, D.; Anderson, P.S.; Huff, J.R. *J. Med. Chem.* 1994, 37, 3443; (d) Askin, D.; Eng, K.K.; Rossen, K.; Purick, R.M.; Wells, K.M.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* 1994, 35, 673; (e) Maligres, P.E.; Upadhyay, V.; Rossen, K.; Cianciosi, S.J.; Purick, R.M.; Eng, K.K.; Reamer, R.A.; Askin, D.; Volante, R.P.; Reider, P.J. *Tetrahedron Lett.* 1995, 36, 2195; (f) Vacca, J.P.; Dorsey, B.D.; Schleif, W.A.; Levin, R.B.; McDaniel, S.L.; Darke, P.L.; Zugay, J.; Quintero, J.C.; Blahy, O.M.; Roth, E.; Sardana, V.V.; Schlabach, A.J.; Graham, P.I.; Condra, J.H.; Gotlib, L.; Holloway, M.K.; Lin, J.; Chen, I.-W.; Vastag, K.; Ostovic, D.; Anderson, P.S.; Emini, E.A.; Huff, J.R. *Proc. Natl. Acad. Sci.* 1994, 91, 4096.

For a synthesis, see (a) Meng, D.; Bertinato, P.; Balog, A.; Su, D.-S.; Kamenecka, T.; Sorensen, E.J.; Danishefsky, S.J. J. Am. Chem. Soc, 1997, 119, 10073. For isolation and characterization, see (b) Gerth, K.; Bedorf, N.; Höfle, G. Irschik, H.; Reichenbach, H. J. Antibiotics 1996, 49, 560; (c) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. Angew. Chem. Int. Ed. 1996, 35, 1567. For biological activity, see Bollag, D.M.; McQueney, P.A.; Zhu, J.; Hensens, O. Koupal, L.; Liesch, J. Goetz, M.; Lazarides, E.; Woods, C.M. Cancer Res. 1995, 55, 2325.

its promising anticancer activity.¹⁸ The preparation of **14** (the common name of this compound is [4]-phenylene) helped show that the delocalized bonds of a benzene ring were effectively localized in these compounds, generating the elusive cyclohexatriene unit.¹⁹ This discovery caused scientists to reexamine the underlying principles of aromaticity.



The differing structural features offer unique synthetic problems. When such syntheses are published, the step-by-step reaction sequence used to construct each molecule is reported and, occasionally, a summary of the rationale behind the synthesis. This summary sometimes provides insight into why a target was chosen, but not always. To a chemist searching for a target, inspection of previous work may not be of great value, although a close study of these syntheses will be of enormous value for understanding and devising strategies. The five criteria listed below are often cited as characteristic of important synthetic targets. These may be of value to a chemist who is being introduced to synthesis for the first time. Much of the information gained from examining these criteria may be useful for disconnecting the target. (1) Structural verification; (2) important biological activity; (3) analog generation and studies; (4) structural or topological challenges-fundamental understanding of the nature of bonding and molecules; (5) development of new reactions or reagents.

 ⁽a) Pettit, G.R.; Gaddamidi, V.; Cragg, G.M. J. Nat. Prod. 1984, 47, 1018; (b) Pettit, G.R.; Gaddamidi, V.; Cragg, G.M.; Herald, D.L.; Sagawa, Y. J. Chem. Soc. Chem. Commun. 1984, 1693; (c) Pettit, G.R.; Gaddamidi, V.; Herald, D.L.; Singh, S.B.; Cragg, G.M.; Schmidt, J.M.; Boettner, F.E.; Williams, M.; Sagawa, Y. J. Nat. Prod. 1986, 49, 995 (d) Antitumor Alkaloids, Suffness, M.; Cordell, G.A. The Alkaloids, Vol. XXV, Academic Press, Orlando, FL, 1985, pp 198-212, 338-340 (see p 207). For a review of total syntheses, see (e) Manpadi, M.; Korienko, A. Org. Prep. Proceed. Int. 2008, 40, 107.

The chemical name of 14 is bis-benzo[3,4]cyclobuta[1,2-a:1',2'-c]biphenylene. See (a) Diercks, R.; Vollhardt, K.P.C. J. Am. Chem. Soc. 1986, 108, 3150; (b) Vollhardt, K.P.C.; Mohler, D.L. Adv. Strain Org. Chem. 1996, 5, 121; (c) Schulman, J.M.; Disch, R.L. J. Phys. Chem. A 1997, 101, 5596.

10.2.B. Structural Verification

Despite the power of X-ray crystallography and high field NMR, the structures of many complex natural products were incorrectly reported. Examples, as reported by Weinreb,²⁰ include cylindrospermopsin,²¹ the sclerophytins²² and batzelladine F,²³ where the correct structures were determined by the total synthesis. Weinreb uses the example of lepadiformine to demonstrate



the value of total synthesis for determination of structure of a natural product where the original report gave an incorrect structure.²⁰ Synthesis is used for proof of structure, or sometimes revision of an originally proposed structure as in Yamada and co-worker's synthesis of cladocoran A (**15**),²⁴ which was originally published by Fontana, et al as **16**.²⁵ Structure **15** corresponded exactly to the spectral data of Fontana, and the original

proposed structure **16** differs from **15** in the stereochemical assignments at C7, C12, and C16. Synthesis of the compound allowed the correct structure to be defined, and revised.

Single crystal X-ray crystallography has become a powerful method for determining the structures of complex organic molecules.²⁶ An example where X-ray analysis was invaluable for the structure proof is taken from Qian-Cutrone and coworkers isolation of new antitumor alkaloids, stephacidin A (**17**) and B (**18**), produced by Aspergillus



^{20.} Weinreb, S.M. Acc. Chem. Res. 2003, 36, 59.

21. Heintzelman, G. R.; Fang, W.-K.; Keen, S. P.; Wallace, G. A.; Weinreb, S. M. J. Am. Chem. Soc. 2002, 124, 3939.

- 23. Cohen, F.; Overman, L. E. J. Am. Chem. Soc. 2001, 123, 10782.
- 24. Miyaoka, H.; Yamanishi, M.; Kajiwara, Y.; Yamada, Y. J. Org. Chem. 2003, 68, 3476.
- 25. Fontana, A.; Ciavatta, M..; Cimino, G. J. Org. Chem., 1998, 63, 2845.

^{22. (}a) Bernardelli, P.; Moradei, O. M.; Friedrich, D.; Yang, J.; Gallou, F.; Dyck, B. P.; Doskotch, R. W.; Lang, T.; Paquette, L. A. J. Am. Chem. Soc. 2001, 123, 9021; (b) Overman, L. E.; Pennington, L. D. Org. Lett. 2000, 2, 2683.

For example see (a) Powell, H.M.; Prout, C.K.; Wallwork, S.C. Ann. Rept. Progr. Chem. 1964, 60, 593; (b) Seemann, V. AD 626597, U.S. Govt. Res. Develop. Rept. 1966, 41, 99 [Chem. Abstr. 67: R15845m 1967]; (c) Schredt, E.; Weitz, G. (Ed.) Landoet-Boernster, Group III: Crystal and Solid State Physics, Vol. 5, Pts a & b: Structure Data of Organic Crystals, Springer, New York, 1971; (d) Koyama, H.; Okada, K.; Itoh, C. Acta Crystallogr. Sect. B, 1970, 26, 444.

ochraceus WC76466.²⁷ Extensive analysis using NMR suggested that **18** was a dimeric structure related to **17**. Although all structural fragments were determined, the point at which the monomeric units of **17** were linked to form the dimer could not be established. Single-crystal X-ray analysis established the final structure as **18**, with the relative stereochemistry shown as well as the presence of the nitrone and hydroxylamine units.²⁸

It is reasonable to ask why a lengthy synthetic verification might be necessary for a given target when such techniques are available. In many cases, X-ray analysis is not possible due to an unsuitable crystalline form, the unavailability of single crystals, poor morphology of the molecule, or a derivative. In many cases, of course, the molecule does not form a crystalline derivative at all, although crystalline derivatives can sometimes be prepared. As noted for volubilide, even high-field NMR techniques often fail to give the absolute stereochemistry of all chiral centers, although the relative stereochemistry may be discerned. Chemical degradation used in conjunction with spectroscopy is also an important identification protocol but is not successful in every case. Total synthesis and comparison with an authentic sample therefore remains an important method for final structure determination.

10.2.C. Biological Activity

An obvious reason for total synthesis is the importance of the target in medicine, agriculture or other commercial and humanitarian ventures. An important or interesting molecule is usually isolated from a natural source in very small quantity, as with pancratistatin (13). If the molecule is subsequently shown to possess significant biological activity, additional material may be required for further testing or determination of the structure. The small quantities isolated or the difficulties and expense inherent in gathering natural specimens often prevent collection of sufficient amounts of the natural product. If the molecule is to undergo further biological screening, or be used clinically, total synthesis may be the only means to obtain sufficient material.

An example of a synthesis used to verify a structure or to generate sufficient material for useful purposes is seen in pancratistatin (**13**), an *Amaryllidaceae* isoquinoline alkaloid that was isolated by Pettit et al. from *Pancratium littorale* in 0.039% of the dry weight of the bulbs of *P. littorale*.^{18a,b} It was also isolated from the bulbs of *Zephyranthese grandiflora*, but in only 0.0019% yield.^{18a,b} The natural abundance of **13** reported from these plant sources clearly show that harvesting these plants is a poor source to obtain quantities suitable for testing. In biological testing, pancratistatin is believed to behave similarly to narciclasine, which inhibits protein synthesis in eukaryotic cells²⁹ and exhibits antineoplastic activity in ovarian sarcoma

^{27.} Qian-Cutrone, J.; Krampitz, K. D.; Shu, Y. Z.; Chang, L. P. U.S. Patent 6,291,461, 2001.

Qian-Cutrone, J.; Huang, S.; Shu, Y.-Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S.E.; Gao, Q. J. Am. Chem. Soc. 2002, 124, 14556.

 ⁽a) Rivera, G.; Gosalbez, M.; Ballestra, J.P.G. *Biochem. Biophys. Res. Commun.* 1980, 94, 800; (b) Baez, A.; Vazquez, D. *Biochim. Biophys. Acta* 1978, 518, 95; (c) Barbacid, M.; Vazquez, D. J. Mol. Biol. 1974, 84, 603.

and lymphatic leukemia^{18c} as well as being an antimitotic.^{18c} Pancratistatin is in preclinical development at the National Cancer Institute, "based on its high activity against the M5076 sarcoma system."^{18d} It also exhibited good activity against the P388 leukemia.^{18c} The significant antitumor activity coupled with the small amounts of material available from natural sources have prompted many total syntheses, including those by Danishefsky and Lee,³⁰ Hudlicky and co-workers,³¹ Trost and Pulley,³² Rigby et al.³³ and Kim and co-worker's.³⁴

Synthesis of a complex natural product by a multi-step synthetic route can be very expensive. To produce even one gram of active product can require large quantities of both starting material and time. If the synthetic goal is to produce usable quantities of material at a reasonable cost, this must be factored into the retrosynthetic scheme. If one requires only milligram quantities, greater latitude in the choice of starting materials and reagents is possible.

10.2.D. Analog Studies

A target that has interesting or commercially attractive properties may exhibit deleterious side effects, or be unstable to storage and handling. Subsequent studies often show that structural modification to the basic skeleton gives a molecule with different characteristics and the new molecule becomes the synthetic target.

Chlorothiazide is 2H,1,2,4-benzothiadiazine-7-sulfonamide, 6-chloro-1,1-dioxide (**19**).³⁵ It is a diuretic also used to treat hypertension. Studies "determined that significant alterations in the pharmacological profile would follow changes in the heterocyclic ring rather than the ring

bearing the sulfonamide group."³⁶ Structural modification led to the synthesis of chlorexolone (**20**).³⁷ Conversion of the heterocyclic ring in **19** to the *N*-cyclohexyl lactam



^{30.} Danishefsky, S.; Lee, J.Y. J. Am. Chem. Soc. 1989, 111, 4829.

^{31.} Tian, X.; Hudlicky, T.; Königsberger, K. J. Am. Chem. Soc. 1995, 117, 3643.

^{32.} Trost, B.M.; Pulley, S.R. J. Am. Chem. Soc. 1995, 117, 10143.

^{33.} Rigby, J.H.; Maharoof, U.S.M.; Mateo, M.E. J. Am. Chem. Soc. 2000, 122, 6624.

^{34. (}a) Ko, H.; Kim, E.; Park, J.E.; Kim, D.; Kim, S. J. Org. Chem. 2004, 69, 112; (b) Kim S.; Ko, H.; Kim, E.; Kim, D. Org. Lett. 2002, 4, 1343.

^{35. (}a) Novello, F.C.; Sprague, J.M. J. Am. Chem. Soc. 1957, 79, 2028; (b) Novello, F.C. U.S. Patent 2,809,194 [Chem. Abstr. 52: 2939h 1958]; (c) Hinkley, D.F. U.S. Patent 2,937,169 [Chem. Abstr. 54: 18565i 1960]; (d) Dupont, D.; Dideberg, O. Acta Crystallogr., Sect. B 1970, 26, 1884; (e) Wolff, F.W.; Basabe, J.; Grant, A.; Krees, S.; Lopez, N.; Vicktora, J. Med. Ann. DC, 1971, 40, 98 [Chem. Abstr. 75 : 47093w, 1971]; (f) Tubaro, E., Boll. Chim. Farm., 1963, 102, 505 [Chem. Abstr. 60: 2198b, 1964]; (g) Ford, R.V. Ann. New York Acad. Sci. 1960, 88, 809 [Chem. Abstr. 61:12493d, 1964]; (h) Sorice, F., Policlinico (Rome), Sez. Prat. 1960, 67, 625 [Chem. Abstr. 55: 14692cd 1961].

^{36.} Lednicer, D.L.; Mitscher, L.A., Organic Chemistry of Drug Design, Vol. 1, Wiley, 1977, p 321.

^{37.} May & Baker Ltd., Belg. Patent 620,654 [Chem. Abstr. 59: P11436c 1963].

moiety in **20** resulted in improved hypotensive action³⁸ and diuretic action, but did not increase urinary pH or urinary bicarbonate excretion relative to **19**.³⁹ Synthetic modification of a known structure can identify a synthetic target.

Another rationale for preparing analogs of a given target is to study the structurebiological activity profile of a molecule. Flavone 8-acetic acid (**21**) was believed to have potential as an antitumor agent.⁴⁰ Denny and co-workers showed that 9-oxo-9H-xanthene-4-acetic acid (**22a**) is as active



as **21** against colon-38 tumors in mice, and is more dose potent.⁴¹ It was also shown that small lipophilic substituents at the 5-position (see **22b** and **22c**) enhanced dose potency.⁴² A systematic study⁴³ of synthetic derivatives of **22** showed that many related derivatives possessed enhanced antitumor activity, which is a typical case in which a known compound was structurally modified based on structure-activity properties of a related compound. The impetus for this synthesis was therefore a search for a more potent and efficacious drug.

10.2.E. Structural Challenges

Occasionally, a molecule presents such a structural and chemical challenge that its potential as a target is irresistible. Such a synthesis often pushes back the limits of known chemistry for making carbon-carbon bonds, and gives insight into structure, bonding, or fundamental reaction properties of organic molecules.

Paquette and co-workers synthesized dodecahedrane (23),^{44a} and the topology (shape, structural features) of 23 is essentially that of a ball. Having the form of a dodecahedron, first described as one of five regular polyhedra in 400-350 B.C.E. in Plato's *Timaeus*, 23 has a spherical superpolycyclopentanoid topology^{44b} that possesses the highest known point group symmetry (I_n , icosahedral).^{44a} It also



 ⁽a) Maxwell, D.R.; McLusky, J.M. Nature 1964, 202, 300; (b) Bayeli, P.F.; Montagnani, M.; Zampetti, L.P.; Antonelli, A. Boll. Soc. Ital. Biol. Sper. 1969, 45, 406 [Chem. Abstr. 73: 2550k 1970]; (c) Patterson, R.R.; Macaraeg, Jr., P.V.J.; Schrogie, J.J. Clin. Pharmacol. Ther. 1969, 10, 265 [Chem. Abstr. 70: 95348b 1969].

^{39.} Baba, W.L.; Lant, A.F.; Wilson, G.M. Clin. Pharmacol. Therap. 1966, 7, 212 [Chem. Abstr. 64: 18220h 1966].

^{40. (}a) Smith, G.P.; Calveley, S.B.; Smith, M.J.; Baguley, B.C. Eur. J. Cancer Clin. Oncol. 1987, 23, 1209 [Chem. Abstr. 108:15894s 1988]; (b) Ching, L.-M.; Baguley, B.C. Ibid. 1989, 25, 821 [Chem. Abstr. 111:33243v 1989]; (c) Idem. Ibid. 1989, 25, 1513 [Chem. Abstr. 112:15992e 1990]; (d) Zwi, L.J.; Baguley, B.C.; Gavin, J.B.; Wilson, W.R. J. Natl. Cancer Inst. 1989, 81, 1005.

^{41.} Rewcastle, G.W.; Atwell, G.J.; Baguley, B.C.; Calveley, S.B.; Denny, W.A. J. Med. Chem. 1989, 32, 793.

^{42.} Atwell, G.L.; Rewcastle, G.W.; Baguley, B.C.; Denny, W.A. J. Med. Chem. 1990, 33, 1375.

^{43.} Rewcastle, G.W.; Atwell, G.J.; Zhuang, L.; Baguley, B.C.; Denny, W.A. J. Med. Chem. 1991, 34, 217.

 ⁽a) Ternasky, R.J.; Balogh, D.W.; Paquette, L.A. J. Am. Chem. Soc. 1982, 104, 4503; (b) Mehta, G. J. Sci. Ind. Res. 1978, 37, 256.

shows a unique encapsulation of a cavity incapable of solvation, negligible angle strain but great torsion strain,⁴⁵ twenty symmetry equivalent methine units and an absence of structurally allied substances. Paquette was the first to synthesize this molecule, and the creative and sometimes novel chemistry arising from the synthetic solution to targets such as **23** can usually be applied to other synthetic endeavors.

10.2.F. New Reactions and New Reagents

During a total synthesis, completion of a key transformation via known chemical reactions may be impossible. Development of new methodology or modification of existing reactions must be accomplished to give the desired transformation and complete the synthesis. Once developed, later work often shows the reagents developed for that synthesis can be utilized for a variety of other purposes (recall Corey's and Deslongchamps' analyses). An example is the total synthesis of vitamin B-12 (24) reported by Woodward and Eschenmoser.⁴⁶ Late in this synthesis, a key step required hydrolysis of an amide in an intermediate possessing six ester moieties. The reagent used in this transformation was an α -chloronitrone (25), which gave a vinyl nitronium ion (26) when treated with silver ion.



45. Ermer, O. Angew. Chem. Int. Ed. 1977, 16, 411.

46. Woodward, R.B. Pure Appl. Chem. 1973, 33, 145 (pp 171-173).

Reaction with the amide gave 27. Hydrolysis of 27 gave the acid, allowing the synthesis of 24 to be completed. Some years later, Eschenmoser developed a series of transformations using derivatives of the α -chloronitrone described above. Nitrone 28 was used as a diene partner in a Diels-Alder reaction (secs. 11.4.A, 11.7), and the resultant cycloadduct (31) was transformed into several synthetically useful molecules. The secondary product that competed with the cycloaddition was the addition product (29), which was also converted to synthetically useful products. Note that the end-products include furan and alkyne derivatives⁴⁷ when the addition partner is changed from alkenes to alkynes to other derivatives. In the specific example shown, cycloaddition of methylcyclohexene and 28 gave the addition product (31) was formed in 30% yield. This sequence illustrates how a reagent developed for one purpose can be a powerful reagent in a completely different application. Indeed, the discovery of such new reagents and transformations is commonly the result of a total synthesis.



To summarize, the criteria discussed for target selection can be useful during a search for possible molecules to synthesize. They may also offer insights into possible applications to chemical problems that may arise. An understanding of the history of a target and how it is used often provides clues to its chemistry and physical properties. These are essential to execution of a synthesis, if not the actual retrosynthetic analysis.

10.3. RETROSYNTHESIS

When a target is chosen, there are guidelines that allow its systematic disconnection to a starting material. The process that develops this roadmap of synthetic intermediates is called retrosynthesis. This section will describe several ways to analyze a molecule, with the goal of identifying key bonds for disconnection.

^{47. (}a) Shatzmiller, S.; Gygax, P.; Hall, D.; Eschenmoser, A. *Helv. Chim. Acta* 1973, 56, 2961; (b) Kempe, U.M.; Das Gupta, T.K.; Blatt, 'K.; Gygax, P.; Felix, D.; Eschenmoser, A. *Ibid.* 1972, 55, 2187 (c) Gygax, P.; Das Gupta, T.K.; Eschenmoser, A. *Ibid.* 1972, 55, 2205; (d) Das Gupta, T.K.; Felix, D.; Kempe, U.M.; Eschenmoser, A. *Ibid.* 1972, 55, 2198; (e) Petrzilka, M.; Felix, D. Eschenmoser, A. Ibid. 1973, 56, 2950; (f) Shatzmiller, S. Eschenmoser, A. *Ibid.* 1973, 56, 2975.

10.3.A. The Disconnection Approach

Once a synthetic target has been chosen, reactions must be developed that will allow the total synthesis to be accomplished. The choice of a starting material (the molecule, purchased or readily prepared, that is used in the first reaction of the synthetic sequence) is critical. How does one analyze a target in order to determine the best starting material? The answer to that question is the essence of total synthesis, and its answer requires: (1) a detailed analysis of the structure of the target, (2) an excellent knowledge of chemical reactions, (3) a good understanding of stereochemistry, bonding, and reactivity, and (4) a well-developed chemical intuition. This information is then used to **disconnect** bonds in the target, simplifying the structure along reasonable chemical reaction pathways.¹ Wipke and Howe⁴⁸ defined the important bonds that are disconnected, as approached by the computer program LHASA (sec. 10.4.B) developed by Corey and co-workers for analysis of retrosynthetic pathways:^{49,69} Their definition was "There are usually certain bonds in a molecule whose disconnection in the retrosynthetic direction leads to a significant simplification of the ... structure. These are termed strategic bonds." If one of these bonds is to be disconnected, a reaction (or sequence of reactions) must be available that will chemically form that bond in the synthesis. Subsequent simplifications (disconnections) lead ultimately to a molecule that can be recognized as commercially available, available by simple chemical techniques or already prepared by others. This process of structural simplification via disconnection leads to a series of molecular fragments that serve as key intermediates, and each is a synthetic target. Such intermediates allow the synthetic chemist to mentally bridge the starting material with the final target in a logical and sequential manner. This process allows the construction of a **synthetic tree**, for which chemical reactions must be provided to accomplish the planned transformations.

An online synthetic tree for a very simple molecule is presented by the Helsinki University of Technology, as shown in Figure 10.1,⁵⁰ similar to more general synthetic trees presented elsewhere.^{51,159} The target (T_0) is disconnected to "a logically restricted set of structures which may be converted in a single synthetic operation (a chemical step) to the synthetic target."¹² This gives the disconnection product in the first retro-reaction. The subtree represents further disconnection of one branch of the synthetic tree. After several retro-reactions, the synthetic tree will yield several starting materials from one or more of the first branches, which can then be used to construct the molecule. Working *backwards* toward the starting material in the manner illustrated in Figure 10.1 is termed **retrosynthesis**.¹ Each succeeding structure has been modified and always simplified. Bonds have been disconnected, and functional

^{48.} Wipke, W.T.; Howe, W.J. Computer Assisted Organic Synthesis, American Chemical Society, Washington, 1971.

^{49. (}a) Corey, E.J.; Howe, W.J.; Pensak, D.A. *J. Am. Chem. Soc.* **1974**, *96*, 7724; (b) Corey, E.J.; Wipke, W.T.; Cramer, III, R.D.; Howe, W.J. J. Am. Chem. Soc. **1972**, *94*, 421; (c) Corey, E.J.; Jorgensen, W.L. *Ibid.* **1976**, *98*, 189.

^{50.} Helsinki University of Technology, Laboratory of Organic Chemistry. See http://www.hut.fi/Yksikot/ Orgaaninen/Opetus/

^{51.} Ottenheijm, H.C.J. Janssen Chimica Acta 1984, 2, 3.
groups transformed until the relatively simple starting materials shown were obtained. The term **disconnection**^{52,12} therefore refers to "mentally breaking bonds to give successively more simple precursor molecules, but always in a manner in which those bonds can be reformed by known or reasonable chemical reactions." Warren has described this approach in great detail.⁵²



Figure 10.1. A Synthesis Tree.

Massanet and co-workers provided an example of the disconnection analysis as applied to a real synthetic problem, in a synthesis of thapsigargin (**32**).⁵³ In Figure 10.2, the retrosynthesis analysis begins with clipping the labile lactone ring to give **33**. The next disconnection leads to fragment **34**, in which an isopropenyl unit is the precursor to the lactone-diol moiety. This fragment is, in turn, disconnected to give fragment **35** indicates that no new carbon atoms are incorporated, but rather indicates a reorganization (in this case a rearrangement reaction). The final disconnection of **35** leads to two fragments (**36** and **37**), which are either commercially available or readily prepared. This analysis is outlined in the box and shows how a molecule is simplified into smaller, and more manageable fragments by a series of disconnections. Each fragment is prepared and the molecule assembled, following what is essentially the reverse of the retrosynthetic sequence shown. Analysis and simplification of a complex target using this approach is the essence of retrosynthesis.

^{52.} Warren, S., *Designing Organic Syntheses: A Programmed Introduction to the Synthon Approach*, John Wiley, New York, **1978**.

^{53.} Manzano, F.L.; Guerra, F.M.; Moreno-Dorado, F.J.; Jorge, Z.D.; Massanet, G.M. Org. Lett. 2006, 8, 2879.



Figure 10.2. Massanet and Co-worker's Retrosynthetic Analysis of Thapsigargin, 32.

A decision must be made concerning the relative priority of simplification versus controlling the stereochemistry of the stereogenic center, which was not made clear in the above analysis. The analysis of target **32** must include the reality of choosing a method to chemically form that bond in the context of the remaining functionality and stereochemistry. There is not necessarily one correct answer, but rather several possibilities, each with its strengths and weaknesses.

10.3.B. The Problem of Complex Targets

The disconnection of truly complex targets raises the level of difficulty to a higher level of analyses. Isobe and Hamajima's synthesis of the right hand segment of ciguatoxin (**38**) makes the point, where the retrosynthesis shown in Scheme 10.1 was given in the paper.⁵⁴ For the salient reactions of the synthesis, the reader referred to the paper, but several features are clear. First, the initial disconnection of ring F generates two fragments (**39** and **40**). Kira and Isobe had previously synthesized fragment **39**,⁵⁵ and the reader is referred to that work for the retrosynthetic analysis and the actual synthesis. Refunctionalization of fragment **40** gave **41**, and disconnection of ring H led to **42**. Disconnection of ring I gave **43**, which set up the disconnection to **44** and **45**. In this paper, **44** was prepared and coupled with **45**, which was prepared from a key intermediate that was synthesized in a previous paper by Isobe and coworkers⁵⁶ The retrosynthetic analysis involves many parts, detailed analysis of protecting groups and specific reactions, and requires independent syntheses of the fragments. The complexity of the target is reflected in the retrosynthetic analysis, which includes not only reactions and functionality, but also stereochemistry.

^{54.} Hamajima, A.; Isobe, M. Org. Lett. 2006, 8, 1205.

^{55.} Kira, K.; Isobe, M. Tetrahedron Lett. 2001, 42, 2821.

^{56.} Baba, T.; Huang, G.; Isobe, M. Tetrahedron 2003, 59, 6851.



Scheme 10.1. Isobe's Retrosynthetic Analysis of a Portion of Ciguatoxin, 38.

Stereocenters are usually quite important in the total synthesis of complex targets, but not always. Indeed, some targets have no stereocenters, but construction of the molecule by making key bonds and incorporation of substituents and/or functional groups can be quite challenging. A relatively simply example in Scheme 10.2 is taken from Kelly and co-worker's synthesis of pterocellin A (46),⁵⁷ and the first disconnection generates 47 by clipping the five-membered ring (an intramolecular coupling reaction for the synthesis). The next disconnection generates three fragments (48-50), two pyridine fragments and a functionalized acyl fragment. Fragments 48 and 49 are combined to give 51 as the next disconnection fragment, which can be prepared from the commercially available kojic acid (52). The fragment 50 is prepared from the commercially available kojic acid (52).

^{57.} O'Malley, M.M.; Damkaci, F.; Kelly, T.R. Org. Lett. 2006, 8, 2651.

the synthesis must accommodate making the key bonds as well as positioning the heteroatoms and substituents at the proper positions.



Scheme 10.2. Kelly and Co-worker's Retrosynthetic Analysis of Pterocellin A, 46.

10.3.C. Consecutive versus Convergent Syntheses

Any synthetic strategy must describe how to proceed from starting material to product. One can work backwards linearly from the target to a starting material. Alternatively, disconnection can branch to several fragments, each with its own starting material. These fragments can be combined in a non-linear fashion to prepare the target. A synthesis based on a linear pathway is called a consecutive synthesis, and a synthesis based on a branching pathway is called a **convergent synthesis**. In a convergent synthesis the several pieces of a molecule are synthesized individually, and the final target is sequentially assembled from the pieces. This approach differs from a consecutive synthesis, in which the target is assembled step by step from a single starting material until the final target is reached. These two approaches are illustrated in Figure 10.3,⁵⁸ which was used by Velluz et al. to describe their synthetic approach. It appears that the convergent synthesis should have fewer steps in the overall synthesis. In this example, if each step has a mean yield of 90%, the yield of final product after 15 steps is $(0.9)^{15}$ ≈ 0.21 (21%). If the largest sequence is split and divided into convergent solutions, there would be only four consecutive steps $(A_1 \rightarrow B_1 \rightarrow C_1 \rightarrow D_1 \rightarrow Z)$ in a perfectly convergent *pathway.* The yield of the final product would be $(0.9)^4 \approx 0.66$ (66%). It is difficult to achieve such a perfect convergence since functional group manipulation, steric considerations and asymmetric structural features lead to imperfections.⁵⁸ Hendrickson's SYNGEN approach to synthesis (sec. 10.10.A) relies on a convergent synthetic strategy, and will be described later.

^{58.} Velluz, L.; Valls, J.; Mathieu, J. Angew. Chem. Int. Ed. 1967, 6, 778.



Figure 10.3. Consecutive versus convergent syntheses. [Reproduced with permission from Velluz, L.; Valls, J.; Mathieu, J. *Angew. Chem. Int. Ed.* **1967**, *6*, 778. Copyright 1967 VCH Weinheim.]

Massanet and Co-worker's retrosynthetic analysis of thapsigargin, **32**, in Figure 10.2 is one example of a consecutive synthesis. Another consecutive synthesis is shown in Scheme 10.3, in which Selvakumar and Rajulu⁵⁹ converted 2-fluoronitrobenzene **54** to paniculidine B (**59**), in 8 linear steps with an overall yield of 22.7%. Nucleophilic aromatic substitution (sec 2.11.C) followed by a Knoevenagel-type condensation (sec. 9.4.B.iii) converts **54** to the diester **55**. A previously reported rearrangement to **56**⁶⁰ was followed by decarboxylation (sec. 2.9.D) and reduction of the cyano group to the aldehyde in **57** with diisobutylaluminum hydride (sec. 4.6.C). A Barbier-type addition (sec. 8.4.C) gave alcohol **58**, and hydroboration-oxidation (sec. 5.4.A) gave paniculidine B, **59**. Although **59** is not structurally complex, this consecutive synthesis illustrates the fundamental idea of beginning with a single compound and transforming it directly to the target. Another consecutive synthesis is Corey and coworker's synthesis of longifolene in Scheme 10.4.



Scheme 10.3. Selvakumar's Consecutive Synthesis of Paniculidine B (59).

Both Isobe's and co-worker's synthesis of ciguatoxin (**38**, Scheme 10.1) and Kelly and co-worker's synthesis of pterocellin A (**46**, Scheme 10.2) illustrate convergent syntheses. Disconnection to separate fragments requires that each fragment be synthesized independently, and then those fragments are joined in one or more key steps to complete the synthesis. This

^{59.} Selvakumar, N.; Rajulu, G.G. J. Org. Chem. 2004, 69, 4429.

^{60.} Selvakumar, N.; Reddy, B.Y.; Azhagan, A.M.; Khera, M.K.; Babu, J.M.; Iqbal, J. Tetrahedron Lett. 2003, 44, 7065.

fact is quite clear in the retrosynthetic analyses presented for **38** and for **46**. The reader is referred to the cited papers for more details of these examples.

Both consecutive and convergent strategies can be attractive, depending on the target and only careful consideration of each will yield the best approach for an individual target. Obviously, once it is completed a given synthesis can be continually reexamined and, in principle, improved upon. In general, a convergent strategy is expected to produce larger amounts of the target in the fewest steps if a scheme can be devised that converges at a useful point. A symmetrical convergent strategy is often the most attractive⁶¹ (also see sec. 10.10.A).

10.4. SYNTHETIC STRATEGIES⁶²

10.4.A. Defining Various Strategic Approaches

Over many years, E.J. Corey and co-workers have described an elegant approach to the synthesis of complex targets that was incorporated in the computer program LHASA (sec. 10.4.B). The purpose of that program is to assist the analysis of complex synthetic targets.^{48,12,63} The monograph by Corey and Cheng¹ describes approaches for constructing a synthetic tree, and also the logic used for that construction. These modifications include:¹² (1) interconversion, removal, or introduction of functional groups, (2) extension of the atomic chains or appendages, (3) generation of atomic rings, (4) rearrangement of chain or ring members, and (5) cleavage of chains or rings. Each chemical fragment in the synthetic tree must possess chemical properties that are predictable and allow selective combination in only one of many possible modes.^{1,12}

Corey and Wipke described three methodologies for synthesis: direct associative, intermediate associative, and logic centered.¹² The direct associative approach disconnects the target (such as 60)¹² at bonds that generate a structure easily recognized by the chemist. Compound 60, for example, gives easily recognized fragments based on well-known reactions. A retro Diels-Alder reaction (sec. 11.5.B) gave 61 and 62. Hydrolysis of the ester and amide units gave 63-65. This approach is somewhat limited.

^{61.} Bertz, S.A. J. Chem. Soc. Chem. Commun. 1984, 218.

^{62.} See Tatsuta, K.; Hosokawa, S. Chem. Rev. 2005, 105, 4707.

^{63.} Corey, E.J.; Long, A.K.; Rubenstein, S.D. Science 1985, 228, 408.



The intermediate associative approach recognizes a major subunit in the target that corresponds to a known, or potentially available starting material. The choice of this starting material directs the retrosynthetic analysis along a specific pathway.¹² The scope and rigor of solutions to the problem are sometimes very limited, however.¹² Sarett's synthesis of cortisone (**6**)⁶⁴ used deoxycholic acid as a starting material, available as an intermediate, taken from Kendall and co-worker's previous synthesis of 11-keto-etiolithocholic acid.⁶⁵ This earlier synthesis required a total of 30 steps, but Sarett's second synthesis was shorter, and introduced a general method for introduction of the 17 α hydroxyl group.⁶⁶



The logic centered approach leads to a restricted set of structures that may be converted in a single step to the target. Each new structure can, in turn, be converted to a new structure. The purpose of the retrosynthetic analysis is to generate synthetic intermediates (the synthesis tree) that terminate with a number of starting materials.⁶³ Corey et al. outlined this approach in 1964, in the synthesis of longifolene (**67**), which is shown in Scheme 10.4.⁶⁷ This synthesis used the **Wieland-Miescher ketone** (**66**) as the starting material.⁶⁸ Analyses of targets such as longifolene begin with a search for key structural features that may be structurally significant. These key features are¹² (*1*) individual molecular chains, rings, and appendages, (*2*) individual

^{64. (}a) Sarett, L.H. J. Biol. Chem. 1946, 162, 601; (b) Fieser, L.F. Fieser, M. Steroids, Van Nostrand Reinhold, New York, 1959, pp 640-650.

^{65.} McKenzie, B.F.; Mattox, V.R.; Engel, L.L.; Kendall, E.C. J. Biol. Chem. 1948, 173, 271.

^{66. (}a) Sarett, L.H. J. Am. Chem. Soc. 1948, 70, 1454; (b) Sarett, L.H. Ibid. 1949, 71, 2443.

Corey, E.J.; Ohno, M.; Mitra, R.B.; Vatakencherry, P.A. J. Am. Chem. Soc. 1964, 86, 478; (b) Corey, E.J.; Mitra, R.B.; Uda, H. Ibid. 1964, 86, 485.

^{68.} Wieland, P.; Miescher, K. Helv. Chim. Acta 1950, 33, 2215.



functional groups, (3) asymmetric centers and attached groups, and (4) chemical reactivity.

Scheme 10.4. Corey's synthesis of longifolene (67).

The next goal is to reduce molecular complexity. This is done by meeting the following goals:¹² (1) simplification of internal connectivity by scission of rings, (2) reduction of molecular size by disconnection of chains or appendages, (3) removal of functionality, (4) modification or removal of sites of unusually high chemical reactivity of instability, and (5) simplification of stereochemistry. There are also certain transformations that are important adjuncts to these goals but do not simplify the molecule. Examples of these transformations are:¹² (1) functional group interchanges, (2) introduction of functional groups, (3) modification of functional groups to control the level of chemical reactivity, (4) introduction of groups that permit stereochemical or positional control, and (5) internal rearrangement. Above all, the disconnections must lead to chemical reactions that will allow construction of the target. The basic mechanistic aspects of these reactions must be well understood, since the reaction pathway is the same in the forward and reverse directions (principle of microscopic reversibility).¹² If a set of disconnections is found to correlate with a mechanistically sound set of chemical reactions in the forward directions, those steps are taken as part of the synthetic tree. In all steps, stereochemical and topological aspects must be considered.

In an analysis of a target, the vast body of Organic chemistry may lead to the generation of retrosynthetic trees that are too large to be manageable, and include numerous dead ends.⁶³ It is essential that simplification techniques, search strategies, screening procedures and logical analysis be employed as the tree is constructed. If subunits of the molecule that are potential

synthons (the disconnection products often taken as the chemical building blocks) can be found, a strong measure of control over tree branching is possible.^{63,69} The retrosynthetic transform and synthetic reaction to accomplish that transform are intricately linked. Just as the power of a transform to simplify a structure is critically important, the most powerful synthetic reactions are those that reliably increase molecular complexity.⁶³ Transforms that decrease or increase the molecular complexity of a target are important in the retrosynthetic strategy. Bertz described the importance of molecular complexity in the context of synthetic analysis, particularly as applied to convergent syntheses,⁷⁰ a topic also addressed by Merrifield and Simmons.^{70d} Bertz suggested that "topological complexity, as well as other sources of molecular complexity, be examined *in addition* to the classical considerations of synthetic efficiency when evaluating synthetic routes."^{70a}

From the preceding discussions it is clear that there are many approaches for a disconnection approach that constructs a synthesis tree. Corey et al. described five different strategies for retrosynthetic analysis:⁶³

- (1) Transform based strategies. Identify a powerful transform for a specific target that produces a reasonable line in the synthetic tree. Two or three powerful simplifying transforms can be applied successively to the target structure. Alternatively, the same simplifying transforms can be repeatedly applied.⁷¹
- (2) Structure goal strategies. Identify a potential starting material, building block, retrosynthetic subunit, or initiating chiral element (see the chiral template approach in sec. 10.9).
- (3) **Topological strategies**. Identify one or more bonds whose disconnection can lead to major molecular simplification, which is the essence of the strategic bond approach⁷² to be discussed in Section 10.5. These bonds may be in bridged or fused ring cyclic systems or appear as connectors to appendages at rings, functional groups, or stereocenters.
- (4) Stereochemicalstrategies. Heuristically derived procedures for reducing stereochemical complexity in the retrosynthetic direction, these procedures remove stereocenters and take advantage of steric screening or proximity to a functional group. The latter may allow simplification of the target by application of functional group removal transforms.⁷³ Corey defines heuristic as "a noun to mean heuristic principle, a 'rule-of-thumb', which may lead by a shortcut to the solution of a problem or may lead to a blind alley."^{49b}

^{69.} Corey, E.J. Quart. Rev. Chem. Soc. 1971, 25, 455.

^{70. (}a) Bertz, S.H. J. Am. Chem. Soc. **1982**, 104, 5801; (b) Idem, bid., **1981**, 103, 3599; (c) Idem J. Chem. Soc. Chem. Commun. **1981**, 818; (d) Merrifield, R.E.; Simmons, H.E. Proc. Natl. Acad. Sci, USA **1981**, 78, 1329, 692.

^{71.} Corey, E.J.; Long, A.K. J. Org. Chem. 1978, 43, 2208.

^{72.} Corey, E.J.; Howe, W.J.; Orf, H.W.; Pensak, D.A.; Petersson, G. J. Am. Chem. Soc. 1975, 97, 6116.

^{73.} For a synthetic example, see Corey, E.J.; Arnett, J.F.; Widiger, G.N. J. Am. Chem. Soc. 1975, 97, 430.

(5) Functional group oriented strategies. When one or more functional groups are related to an interconnecting atom path, a simplifying transform can often be found. Interconversion, addition, or removal of functionality can pave the way for further retrosynthetic simplification. Both internal protection of functional groups and replacement of a highly reactive group by another less reactive equivalent can be useful.⁷⁴

10.4.B. LHASA

Corey and co-workers developed a computer program that uses the strategies described above in a way that emulates the most effective problem solving approaches of a synthetic chemist, with an emphasis on complex rather than routine synthetic problems. This computer program is called **LHASA** (Logic and Heuristics Applied to Synthetic Analysis; see sec. 1.5.D). It analyzes a molecule, develops retrosynthetic schemes and supplies appropriate chemical reactions. Wipke and Howe provide a useful description of this program:⁴⁸

"One important aspect of the project has been the writing of a general purpose computer program which will aid the laboratory chemist and will employ both the basic and more complex techniques for synthetic design as elucidated by this study. The program (hereafter also called **LHASA**) is intended to propose a variety of synthetic routes to whatever molecule it is given. The responsibility for final evaluation of the merit of the routes lies with the chemist. The program is to be an adjunct to the laboratory chemist as much as any analytical tool."⁴⁸

LHASA is an interactive program that displays the target, allowing the chemist to select a synthetic strategy (or strategies). The program then suggests synthetic routes that satisfy the goals of the selected strategy.⁶³ The analysis generates retrosynthetic precursors and generates a synthetic tree (see Figure 10.4).⁶³ The chemist takes responsibility for choosing strategies and tactics and for deciding which precursors should be submitted to LHASA for further simplifications. LHASA selects the actual transforms, based on a database of known reactions.

Portions of a typical LHASA analysis are shown in Figure 10.4.⁷⁵ A LHASA transform is shown in part (*a*), in this case based on the Fries rearrangement (see sec. 12.5.E). In part (*b*), a target molecule is shown (**Target 3**), and a retrosynthesis is provided that is based toward acetophenone. Note that a description of the projected chemistry is shown over each disconnect arrow. In part (*c*), a retrosynthetic tree is shown as part of the analysis of a target, where the numbers represent chemical structures generated by LHASA. In part (*d*), a specific retrosynthetic analysis is shown in which one unit, the hydroxymethyl group, is removed from Target 3, with the projected reaction being an organometallic transform. The data provided by Figure 10.4 is meant to illustrate the type of information that is available from the LHASA program. A sample retrosynthesis for aphidicolin is shown in Figure 10.5, taken from the work

^{74.} Corey, E.J.; Orf, H.W.; Pensak, D.A. J. Am. Chem. Soc. 1976, 98, 210.

^{75. (}a) Johnson, A.P.; Marshall, C.; Judson, P.N. J. Chem. Inf. Comput. Sci. 1992, 32, 411. Also see (b) Johnson, A.P.; Marshall, C. J. Chem. Inf. Comput. Sci. 1992, 32, 418.

of Corey and co-workers.76



Figure 10.4. Portions of a LHASA transform and retrosynthetic analysis. (a) Display of LHASA transform. (b) Retrosynthesis of **Target 3** to acetophenone. (c) Part of the tree from the retrosynthetic analysis of target. (d) Retrosynthetic removal of the hydroxymethyl group from **target 3** by a route involving an organometallic addition transform. [Reprinted from Johnson, A.P.; Marshall, C.; Judson, P.N. J. Chem. Inf. Comput. Sci. **1992**, 32, 411. Copyright[©] 1992 by the Amer. Chem. Soc.]



Figure 10.5. A LHASA-generated retrosynthetic pathway for the synthesis of aphidicolin. [Reprinted from Corey, E.J.; Long, A.K.; Lotto, G.I.; Rubenstein, S.D. *Recl. Trav. Chim. Pays-Bas* 1992, 111, 304.]

Note that a variation of this computer technique has been developed, with the goal of synthesis simplification. "Mathematics Applied to Synthetic Analysis (MASA) is a useful addition to Logic and Heuristics Applied to Synthetic Analysis (LHASA), as it can be used to calculate the simplification afforded by alternative disconnections of a target molecule. One-bond and two-bond disconnections that are more efficient as far as simplification is concerned than those

^{76.} Corey, E.J.; Long, A.K.; Lotto, G.I.; Rubenstein, S.D. Recl. Trav. Chim. Pays-Bas 1992, 111, 304.

identified by the LHASA criteria have been found by using MASA."⁷⁷ This approach is based on identifying topological strategic bonds.

10.5 THE STRATEGIC BOND APPROACH

Several available strategies can be applied to the specific task of breaking the first (and subsequent) bond(s) in the target. For the student beginning a study of synthesis, a more formalized approach would be useful. Corey and co-workers enumerated several rules that tie together the strategies and goals of retrosynthetic analysis into a **strategic bond analysis**. These rules provide insight into the first disconnection and the complete synthetic tree. The analysis begins with an inspection of the target molecule to determine if the structure is compatible with simple solutions. Before the strategic bonds are determined, simplification may be possible if the molecule possesses symmetry, is structurally similar to another molecule that has been previously synthesized, or has repeating units within the structure.

The following items are only guidelines. These guidelines are a reasonable place to begin planning a synthesis, but by no means the only way to approach a problem. If a disconnection is reasonable and there is either known chemistry or planned chemistry to reconstitute that bond in a synthesis, proceed.

10.5.A. The Preliminary Scan

The analysis inspects the molecule to determine if it can be simplified. There are three criteria.⁷⁸



10.5.A.i. Is There Symmetry or Near Symmetry in Two Parts of the Molecule? If so, the synthesis may be simplified by synthesizing and then joining together the two or more identical pieces. A good example is the molecule C-toxiferin I (68),⁷⁹ which is essentially a dimer. In 68, one-half of the molecule is identical to the other, and it has been shown that treatment with sulfuric acid cleaves the molecule into a single product that regenerates the dimer on treatment

with hot sodium acetate.⁷⁹ Synthesis of one piece and joining the two identical pieces together greatly simplifies an overall synthesis with a built-in convergence.

The symmetry may not be obvious and the target should be carefully analyzed. Usnic acid (73) is an example of a molecule that possesses potential symmetry.⁸⁰ The molecule may not

^{77.} Bertz, S.H.; Rücker, C.; Rücker, G.; Sommer, T.J. Eur. J. Org. Chem. 2003, 4737.

^{78.} Bersohn, M.; Esack, A. Chem. Rev. 1976, 76, 269.

^{79. (}a) Bernauer, K.; Berlage, F.; von Philipsborn, W.; Schmid, H. Karrer, P. *Helv. Chim. Acta* **1958**, *41*, 2293; (b) Berlage, F. Bernauer, K.; von Philipsborn, W.; Waser, P.; Schmid, H. Karrer, P. *Ibid.* **1959**, *42*, 394.

^{80.} Corey, E.J. Pure Appl. Chem. 1967, 14, 19.

be obviously symmetrical, but the symmetry appears upon disconnection and suggests a retro phenolic oxidative coupling (see sec. 13.8.B). The synthesis of usnic acid is shown in Scheme 10.5,⁸¹ with a phenolic oxidative coupling of a single phenol derivative (**69**) to give **71** via coupling of the initial oxidation product **70**. The **phenolic oxidative coupling** reaction (sec. 13. 8.B) is a radical process by which two phenol moieties are joined.⁸² The two phenolic moieties reacted via an acid-catalyzed Michael reaction to give a dimer (**71**), which cyclized via the phenol hydroxyl group to give **72**. Treatment with concentrated sulfuric acid completed the two-step synthesis of **73**. Recognizing the potential symmetry greatly shortened the synthesis.



Scheme 10.5. Phenolic oxidative coupling strategy for the synthesis of usnic acid (73).

10.5.A.ii. Is the Problem Like One Already Solved? Woodward' and co-workers synthesis of reserpine (8) is shown in Scheme $10.6.^{10}$ Compound 74 was important intermediate in that synthesis. Deserpidine (79)⁸³ is a natural product that is structurally similar to 8, but lacking the methoxy group on the indole moiety. It closely mimics the activity of 8,⁸⁴ and a total

^{81.} Barton, D.H.R.; Deflorin, A.M.; Edwards, O.E. J. Chem. Soc. 1956, 530.

 ⁽a) Kotani, E.; Miyazaki, F.; Tobinaga, S. J. Chem. Soc. Chem. Commun. 1974, 300; (b) Barton, D.H.R.; James, R.; Kirby, G.W. Widdowson, D.A. Ibid. 1967, 266; (c) Kametani, T.; Fukumoto, K. Synthesis 1972, 657; (d) Kametani, T.; Yamaki, K. Terui, T.; Shibuya, S.; Kukumoto, K. J. Chem. Soc. Perkin I 1972, 1513.

 ⁽a) Wenkert, E.; Liu, L.H. *Experientia* 1955, 11, 302; (b) Schlittler, E.; Ulshafer, P.R.; Pandow, M.L.; Hunt, R.M.; Dorfman, L. *Ibid.* 1955, 11, 64; (c) Huebner, C.F.; MacPhillamy, H.B.; Schlittler, E.; St. André, A.F. *Ibid.* 1955, 11, 303; (d) MacPhillamy, H.B.; Dorfman, L.; Huebner, C.F.; Schlittler, E.; St. André, A.F. J. Am. *Chem. Soc.* 1955, 77, 1071; (e) Yamamoto, T.; Yamanaka, M. *Shinyaku to Rinsho* 1955, 4, 19 and pp 175 [*Chem. Abstr.* 51: 14984h 1957] and see the other articles cited in this abstract.

^{84.} Lednicer, D.L.; Mitscher, L.A.; Organic Chemistry of Drug Design, Vol. 1, John Wiley, 1977, pp 320-321.

synthesis of **79** was developed by Velluz⁸⁵ and later by Protiva.⁸⁶ Intermediate **75**, prepared from 74 from the Woodward synthesis, was used as the starting material to give the alternative synthesis also shown in Scheme 10.6.86 Reaction of 75 with 6-methoxytryptamine (obtained with great difficulty) gave 76.8 Intermediate 76 was converted to 77, and then to 8. In the synthesis of 79, key intermediate was 78 prepared by reaction of tryptamine with 75. This simple modification of Woodward's synthesis obviously saved Velluz and Protiva the time and effort required to develop a new synthetic approach. This example suggests that thorough familiarization with the target, including knowledge of all previous syntheses of the target and also related compounds (i.e., thorough search of the literature) is always beneficial. One does not always want to mimic a literature approach, but when the target is structurally similar to one that is known, the use of a key intermediate or transformation sequence in designing a retrosynthesis is prudent and usually desirable. Obviously, if one has an improved method or route to a target, the retrosynthesis is biased to include this new method. It is common for a published total synthesis to be followed by several later syntheses that improve or expand upon it. Syntheses developed later are often useful for producing large quantities of the natural product, as the initial sequence may produce only small amounts (milligrams) of the target.

10.5.A.iii. Is the Molecule a String of Available or at Least Simple Pieces? The synthesis⁸⁷ of the macrolide antibiotic nonactin (83)⁸⁸ is a useful example. Nonactin consists of four units of nonactic acid (83),⁸⁸ joined together in a tetrameric ring. A total synthesis would be greatly simplified by preparing 82, since the final synthesis of 83 would require only macrocyclization (formation of a large lactone ring, sec. 6.6.B).⁸⁹ Gerlach and co-worker's synthesis of 83, which is shown in Scheme 10.7,⁸⁷ utilized this approach. The synthetic precursor of 82 was 81, produced in several steps from furanyl derivative 80. Note that when two remote, reactive ends of a molecule must be brought together so reaction can occur, intermolecular processes often dominate (sec. 6.6.B) and the low yield of 83 obtained by Gerlach is a result of such problems, which does not diminish the simplicity of the synthetic approach that recognized

^{85.} Velluz, L.; Muller, G.; Joly, R.; Nominé, G.; Mathieu, J.; Allais, A. Warnant, J.; Valls, J.; Bucourt, R.; Jolly, J. Bull. Soc. Chim. Fr. 1958, 673.

 ⁽a) Weichet, H.; Pelz, K.; Bláha, L. *Collect. Czech. Chem. Commun.* 1961, 26, 1537; (b) Protiva, M.; apek, A.; Jílek, J.O.; Kakác, B.; Tadra, M. *Ibid.* 1961, 26, 1537; (c) Ernest, I.; Protiva, M. *Ibid.* 1961, 26, 1137; (d) Protiva, M.; Rajser, M.; Jilek, J.O. *Monatsh. Chem.* 1960, 91, 703.

 ⁽a) Gerlach, H.; Wetter, H. *Helv. Chim. Acta* 1974, 57, 2306; (b) Gerlach, H.; Oertle, K.; Thalmann, A.; Servi, S. *Ibid.* 1975, 58, 2036.

 ⁽a) Keller-Schierlein, W.; Gerlach, H. Fortschr. Chem. Org. Naturstoffe 1968, 26, 161; (b) Ando, K.; Oishi, H.; Hirano, S.; Okutomi, T. Suzuki, K.; Okazaki, H.; Sawada, M.; Sagawa, T. J. Antibiot. (Tokyo) 1971, 24, 347; (c) Dobler, M.; Dunitz, J.D. Kilbourn, B.T. Helv. Chim. Acta 1969, 52, 2573; (d) Dobler, M. Ibid. 1972, 55, 1371; (e) Iitaka, Y.; Sakamaki, T. Nawata, Y. Chem. Lett. 1972, 1225.

 ⁽a) Taub, D.; Girotra, N.N.: Hoffsommer, R.D.; Kuo, C.H.; Slates, H.L.; Weber, S.; Wendler, N.L. *Tetrahedron* 1968, 24, 2443; (b) Corey, E.J.; Nicolaou, K.C. J. Am. Chem. Soc. 1974, 96, 5614; (c) Masamune, S.; Kim, C.U.; Wilson, K.E.; Spessard, G.O. Georghiou, P.E.; Bates, G.S. *Ibid.* 1975, 97, 3512; (d) Masamune, S.; Yamamoto, H.; Kamata, S.; Fukuzawa, A. *Ibid.* 1975, 97, 3513.



ļ

N

/ H

NH₂

nonactin as a string of repeating fragments.

2. POCl₃, reflux; NaBH₄, MeOH Н N H Н Н MeO Н 1. NaOMe, MeOH, heat 0 N H Н MeO₂C MeO . OMe Н Cl Ac 2. MeO 79 77 MeO₂C Ó . OMe MeO Н N O MeO OMe ÓМе Η MeO Н 'n OMe ÓMe MeO₂C 8 OMe MeO

Н

ŌMe

75

MeO₂C

Scheme 10.6. Syntheses of reserpine (8) and deserpidine (79).

3. MeO

OAc

OMe

MeO₂C

76

MeO₂C

1. NaBH₄

Ν

MeO₂C

MeO₂C

78

'OAc

ŌMe

Ĥ

NH₂

IJ

N

Î H



Scheme 10.7. Gerlach and co-Worker's Synthesis of Nonactin (83)

10.5.B. Criteria for Disconnection of Strategic Bonds

Once the preliminary scan is complete, the next step is to disconnect the molecule by breaking bonds that can be reconnected by known or reasonable chemical steps, to generate the synthetic tree. As discussed above, these important bonds are called strategic bonds. Bersohn has restated Corey's rules to tie together the strategies outlined in Section 10.4.^{78,49} One should not be a slave to these statements but rather treat them as excellent suggestions for how to begin planning a synthesis:

- 1. Labile groups should be removed first.
- **2.** Transforms should remove as much functionality as possible and should remove stereochemical centers where possible.
- 3. Favor transforms that generate closely related intermediates.
- **4.** If a certain substructure interferes with a key process, then use a transform to remove that substructure.
- 5. Where possible, use transforms to build bridges between the goal atoms.
- 6. Convert the molecule under consideration into the product of one of the powerful

reactions.

- **7.** Disconnect appendages attached to atoms bearing certain functional groups such as OH or C=O.
- **8.** Consider all pairs of functional groups in the molecule to ascertain whether known transforms can disconnect any of the intervening bonds.
- 9. In a ring system preferentially disconnect the strategic bonds.

The examples that follow in Section 10.5.B.i-10.5.B.viii will illustrate an application of each of these rules.

10.5.B.i. Remove Labile Groups First. Removing a labile group is illustrated by a retrosynthetic step in Holmes and co-worker's synthesis of (–)-histrionicotoxin, **84**.⁹⁰ The alcohol and conjugated ene-yne units in **84** are quite reactive. Both units are removed in the initial disconnection and replaced with R and R'



groups, which represent functionality that can be elaborated to the conjugated system. In addition, the labile amine and alcohol units are converted to the isoxazolidine unit in **85**. This disconnection allows one to focus on constructing the fundamental spirocyclic ring system, knowing that highly reactive groups will be added last.

10.5.B.ii. Remove Stereochemical Centers. The vast majority of natural products and important synthetic targets are characterized by several stereogenic centers that are often contiguous. A major task of a total synthesis is the generation of these stereogenic centers, in a controlled and predictable manner. It is therefore important to plan all reactions, and often the entire retrosynthesis around stereoselective reactions. Chemical reactions that involve formation of bonds *at* a chiral carbon allow a measure of control over stereochemical induction. The stereogenic center and the reaction center usually have a 1,2-, 1,3-, or occasionally a 1,4-relationship. It is also possible that a remote center is held in close proximity due to a particular conformation, and exerts an influence on the reaction. Molecular or computer modeling is usually necessary



to observe the correct influence of remote centers on a disconnection. Disconnections are, in general, made at a bond connected to a stereogenic center (1,2-relationship) rather than to a bond containing a pendant group that contains a stereogenic center. In

90. Williams, G.M.; Roughley, S.D.; Davies, J.E.; Holmes, A.B. J. Am. Chem. Soc. 1999, 121, 4900.

Paquette and co-worker's synthesis of magellanine (**86**),⁹¹ disconnection of the piperidine ring removed two stereogenic centers, although the allylic alcohol unit introduced another (see **87**). The next disconnection removed the cyclohexenol ring along with two stereogenic centers, and the use of a protected carbonyl (the dithiane) effectively removed the stereogenic center at the secondary alcohol, giving **88**.

10.5.B.iii. Favor Closely Related Intermediates. It is usually preferable to simplify the target molecule in small bites (i.e., prune small branches of the synthesis tree rather than large branches). Moving too far down the synthetic tree with large disconnections will mean that several carbon-carbon bond-forming reactions or functional group exchanges are required to convert one disconnect product to another. It may be difficult to find transforms where several bonds can be formed simultaneously in the synthesis, although such transformations do exist in some cases. For a first analysis, simplification should be done so that a minimum number of carbon-carbon bond-forming reactions and functional group exchanges are required for each disconnect product. In this way, it is easy to understand the simplification and the implications for the requisite chemical reactions, which is illustrated by the relatively simple disconnection sequence used by Kibayashi and co-workers in a synthesis of (-)-(3R, 6S, 9R)decarestrictine C_2 , 89.⁹² The target was first converted to the seco-acid (90), removing the labile ester unit, and disconnection to aldehyde 91 suggests a condensation reaction to make that bond. The last disconnection leads to tetraol 92, again suggesting a condensation reaction. In each case, one key bond is disconnected and the differences between target and disconnect product are structurally close and predictable. Generally, one disconnects one or two bonds per disconnection, but more may be disconnected if the pieces are closely related.



10.5.B.iv. Remove Interfering Substructures. An example provided by Corey and coworkers⁷⁴ is the disconnection of 93 and 95 to 94. Path *a* is a simple epoxidation (sec. 3.4), and path *b* is a Baeyer-Villiger oxidation (sec. 3.6). A cyclic cis alkene moiety such as that in 94 shows moderate reactivity with peroxyacids, but the ketone moiety in 94 is very reactive, since it is strained. Disconnection of 95 to 94 is viable, since the synthesis will proceed without interference from the alkene moiety. Disconnection of 93 to 94, however, requires that the interfering carbonyl be removed in any synthetic attempt. The best retrosynthesis of 93 will probably involve protection of the ketone (sec. 7.3.B), as a ketal for example. In Figure 10.4,⁷⁵ the

^{91.} Williams, J.P.; St. Laurent, D.R.; Friedrich, D.; Pinard, E.; Roden, B.A.; Paquette, L.A. J. Am. Chem. Soc. 1994, 116, 4689.

^{92.} Arai, M.; Morita, N.; Aoyagi, S.; Kibayashi, C. Tetrahedron Lett. 2000, 41, 1199.

LHASA program generated a retrosynthetic sequence with boxes around reactive or interfering functional groups that can be protected and dashed boxes around unstable (interfering) groups that are not easily protected. Quite often, this rule refers to protection of interfering structure.



10.5.B.v. Use Transforms to Bridge Goal Atoms. If a disconnection results in cleavage of the target into separate pieces, chemical reconnection usually requires formation of one to four bonds. Two-bond disconnections are well known, although there are not many of them, and if three or four bonds must be formed it is usually very difficult to rejoin all the bonds in one synthetic step. The Diels-Alder cycloaddition (sec. 11.4.A) is an example in which two bonds are connected. If possible, it is useful to bridge the two pieces together by formation of one of the requisite bonds in the retrosynthesis, bringing the two pieces close enough to allow subsequent formation of the other bond(s). An illustration of this principle is Trost and co-worker's retrosynthetic analysis of ibogamine $(100)^{93}$ in Scheme 10.8 (\Leftarrow represents a retrosynthetic disconnection and \rightarrow represents the synthetic step). The first disconnection of the nine-membered ring gave 99 in which the two disconnected fragments are attached. The proximity of these fragments allows the usually difficult nine-membered ring to be formed in the synthesis. The bridged ring was disconnected to give 98, in which the two fragments are still bridged. Disconnection to 97 gave a fragment (96) that was recognized as a precursor to the starting diene. In the actual synthesis (also in Scheme 10.8), reaction of intermediate 97 with tryptamine gave 98, which bridged the indole and the azabicyclo[2.2.2]octane moieties, allowing formation of 99. The organopalladium reagent used for this coupling will be discussed in Section 12.7. Final joining of the bridged pieces gave 100, completing the total synthesis.



Scheme 10.8. Trost and co-Worker's Synthesis of Ibogamine (100).

^{93.} Trost, B.M.; Godleski, S.A.; Genet, J.P. J. Am. Chem. Soc. 1978, 100, 3930.

10.5.B.vi. Convert the Molecule into the Product of One of the Powerful Reactions. Powerful reactions have been defined as those synthetic reactions that reliably increase molecular complexity. Disconnections that are based on powerful reactions will, therefore, greatly *decrease* the molecular complexity of the target, which is, of course, a major goal of a disconnection strategy. Corey listed several examples of such reactions.⁶³ Synthetic examples of these reactions are shown in Table 10.1.¹²

Table 10.1. Powerful Reactions^a



5. Position Selective Partial Aromatic Reduction



6. Cation ≠ Cyclization



_101

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7. Radical π Cyclization



8. Aldol Condensation



9. Silyl-acyloin Cyclization



10. Internal S_N2 Cyclization



11. Friedel-Crafts Type Cyclization



12. Internal Ene Reaction



13. Cationic Rearrangement



14. Photocyclization



15. Fischer Indole Synthesis



16. Knorr Pyrrole Synthesis



17. [m,n]-Sigmatropic Rearrangement (anionic Oxy-Cope)



18. [m,n]-Sigmatropic Rearrangement (Claisen)



19. Ring-closing metathesis (RCM)



20. Heck Reaction and other Palladium-catalyzed coupling reactions



65%¹¹⁵

^a The listing of reaction types 1-19 is adapted from Corey, E.J.; Wipke, W.T. *Science* **1969**, *166*, 178 by courtesy of Professor E.J. Corey. Copyright 1969 by the AAAS. The specific examples are referenced.

The intermolecular **Diels-Alder reaction** (sec. 11.4) is shown first. Example 1 from Table 10.1 is a carbo-Diels-Alder reaction taken from the catalytic enantioselective synthesis of estrone by Corey and co-workers in 92% yield (94% ee).⁹⁴ Intermolecular and intramolecular versions of this important reaction are known. Example 2 is a quinone Diels-Alder reaction (see Mikami et al. for another example),⁹⁵ taken from the Dallavalle and co-worker's synthesis of topopyrone in which Diels-alder cycloaddition was followed by hydrolysis and elimination to give the product shown in 82% yield.⁹⁶ Example 3 is a hetero Diels-Alder reaction (sec. 11.7), taken from a synthesis of (+)-prelactone C by Kobayashi and co-workers.⁹⁷ A Lewis acid catalyzed cyclization of an aldehyde with the functionalized diene shown, gave the dihydropyran product, which was converted to the enol under the reaction conditions and gave the pyrone in 89% yield and 93% ee. Example 4 is a **Robinson annulation** (sec. 9.7.C) induced by the basic potassium fluoride in a synthesis of norzoanthamine by Theodorakis and co-workers.⁹⁸

Example 5 is taken from Zard and Sharp's synthesis of aspidospermidine,⁹⁹ in which **Birch reduction** (see sec. 4.9.E) of the aromatic ring was followed by alkylation of the intermediate anion and then hydrolysis to give the cyclohexadiene in 85% yield for two steps. Example 6 is a cationic π cyclization reported by Grubbs and Cannizzo,¹⁰⁰ that uses Speckamp's procedure¹⁰¹ (sec. 12.2.C). In Example 7 a radical π cyclization (sec. 13.7), reported by Corey and co-workers in a synthesis of salinosporamide A,¹⁰² generated the silyloxy ring in 89% yield. Example 8 is an **aldol condensation** (sec. 9.4.A) reported by Mehta and Shinde in a synthesis of (+)-minwanenone.¹⁰³ Example 9 used the silyl-acyloin cyclization (sec. 13.8.E) to close the ring in the Sih and co-workers synthesis of castanospermine.¹⁰⁴ Chan and co-workers synthesis of 5'-methoxyhydnocarpin-D used the intramolecular S_N2 displacement (sec. 2.6.A) of the secondary tosylate by the phenolic oxygen nucleophile in Example 10.¹⁰⁵ This transformation was included because it represents those reactions that give one the ability to control relative and absolute stereochemistry because the S_N2 reaction proceeds with inversion

99. Sharp, L.A.; Zard, S.Z. Org. Lett. 2006, 8, 831.

- 102. Reddy, L.R.; Saravanan, P.; Corey, E.J. J. Am. Chem. Soc. 2004, 126, 6230.
- 103. Mehta, G.; Shinde, H.M. Tetrahedron Lett. 2007, 48, 8297.
- 104. Bhide, R.; Martezaei, R.; Scilimati, A.; Sih, C.J. Tetrahedron Lett. 1990, 31, 4827.
- 105. Chan, K.-F.; Zhao, Y.; Chow, L.M.C.; Chan, T.H. Tetahedron 2005, 61, 4149.

^{94.} Hu, Q.-H.; Rege, P.D.; Corey, E.J. J. Am. Chem. Soc. 2004, 126, 5984.

^{95.} Mikami, K.; Motoyama, Y.; Terada, M. J. Am. Chem. Soc. 1994, 116, 2812.

^{96.} Gattinoni, S.; Merlinni, L.; Dallavalle, S.D. Tetrahedron Lett. 2007, 48, 1049.

^{97.} Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. J. Am. Chem. Soc. 2003, 125, 3793.

^{98.} Ghosh, S.; Rivas, F.; Fischer, D.; González, M.A.; Theodorakis, E.A. Org. Lett. 2004, 6, 941.

^{100.} Cannizzo, L.F.; Grubbs, R.H. J. Org. Chem. 1985, 50, 2316.

 ^{101. (}a) Dijkink, J.; Speckamp, W.N. *Tetrahedron Lett.* 1975, 4047; (b) Shoemaker, H.E.; Speckamp, W.N. *Ibid.* 1978, 1515; (c) Speckamp, W.N. *Recl. Trav. Chim. Pays-Bas* 1981, 100, 345.

of configuration (secs. 2.6.A, 6.2, 6.3). Example 11 shows a Friedel-Crafts acylation reaction (sec. 12.4.D) in which the carboxylic acid was first converted to the acid chloride and then treatment with AlCl₃ gave the ketone in 84% yield as part of Sarpong and Simmons synthesis of salviasperanol.¹⁰⁶ Example 12 is an internal carbonyl **ene reaction** (sec. 11.13) taken from the Mori and co-worker's synthesis of (+)-crinamine,¹⁰⁷ which gave the indicated product in 59% yield. In Example 13, Corey and Kingsbury treated the cyclopropylcarbinyl alcohol starting material with trimethylaluminum and observed the rearrangement product shown as part of a synthesis of β -araneosene.¹⁰⁸ In this case, treatment with *p*-toluenesulfonic acid also led to rearrangement but with much lower selectivity. Nicolaou and co-workers A used a Witcop-type photocyclization^{109a,b} (secs. 13.4, 13.7) used a synthesis of diazonamide A, as shown in Example 14.^{109c} In this case, the hexatriene-cyclohexene isomerization is reversible, allowing the cyclization to proceed in the presence of an oxidizing agent such as air.¹¹⁰ Blechert and Jiricek's synthesis of (–)-gilbertine provides an illustration of the **Fischer** indole synthesis (sec. 12.5.C),¹¹¹ shown in Example 15. In Example 16, Lash and Zhang used a Knorr pyrrole synthesis procedure in the synthesis of porphyrin mineral abelsonite and related petroporphyrins.¹¹² An anionic **oxy-Cope rearrangement** (sec. 11.12.C.ii) is shown in Example 17 to illustrate signatropic rearrangement processes (sec. 11.12.A), taken from the Liao and Hsu synthesis of bilosespene A.¹¹³ Example 18 is another sigmatropic rearrangement, the Claisen rearrangement (sec. 11.12.D), in this case used by Brimble and co-workers in a synthesis of γ -rubromycin.¹¹⁴ Increased interest in the ring-closing metathesis reaction is illustrated by Example 19 in the Alibé, de March and co-worker's synthesis of securinine.¹¹⁵ The ability to generate two alkene units in different parts of the molecule and then use them to form a ring certainly makes this reaction worthy of addition to the list of powerful reactions. Finally, palladium-catalyzed coupling reactions have become extremely important in organic synthesis. The Heck reaction, Stille coupling and Suzuki coupling are important variations that will be discussed in chapter 12 (sec. 12.7). Example 20 shows a Heck coupling, taken from a synthesis of hamigeran B by Trost and co-workers.¹¹⁶

108. Kingsbury, J.S.; Corey, E.J. J. Am. Chem. Soc. 2005, 127, 13813.

- 110. Stermitz, F.R. Organic Photochemistry, Vol. 1, Chapman, O.L. (Ed., Marcel-Dekker, New York, 1967, p 247.
- 111. Jiricek, J.; Blechert, S. J. Am. Chem. Soc. 2004, 126, 3534.
- 112. (a) Zhang, B.; Lash, T.D. *Tetrahedron Lett.* 2003, 44, 7253; and see (b) Harbuck, J. ; Rapoport, H. J. Org. Chem. 1971, 36, 853; (c) Knorr, L. Berichte, 1884, 17, 1635; (d) Knorr, L. Annalen 1886, 236, 290; (e) Knorr, L.; Lange, H. Berichte, 1902, 35, 2998.
- 113. Hsu, D.-S.; Liao, C.-C. Org. Lett. 2003, 5, 4741.
- 114. Tsang, K.Y.; Brimble, M.A.; Bremner, J.B. Org. Lett. 2003, 5, 4425.
- 115. Alibés, R.; Ballbé, M.; Busqué, F.; de March, P.; Elias, L.; Figueredo, M.; Font, J. Org. Lett. 2004, 6, 1813.
- 116. Trost, B.M.; Pissot-Soldermann, C.; Chen, I.; Schroeder, G.M. J. Am. Chem. Soc. 2004, 126, 4480.

^{106.} Simmons, E.M.; Sarpong, R. Org. Lett. 2006, 8, 2883.

^{107.} Nishimata, T.; Sato, Y.; Mori, M. J. Org. Chem. 2004, 69, 1837.

 ⁽a) Yonemitsu, O.; Cerutti, P.; Witkop, B. J. Am. Chem. Soc. 1966, 88, 3941; (b) Theuns, H.G.; Lenting, H.B.M.; Salemink, C.A.; Tanaka, H.; Shibata, M.S.; Ito, K.; Lousberg, R.J.J. Heterocycles 1984, 22, 2007; (c) Nicolaou, K.C.; Chen, D.Y.-K.; Huang, X.; Ling, T.; Bella, M.; Snyder, S.A.J.Am. Chem. Soc. 2004, 126, 12888.

The reactions in Table 10.1 are classified as powerful due to the variety of transformations (formation of rings, molecular reorganization, generation of reactive functional groups from relatively unreactive functionality, or for functional group insertion) that were achieved all in essentially one synthetic step. Other reactions could easily be termed powerful, but these are sufficient to illustrate that if a reaction induces extensive and useful structural modifications, the synthetic tree should be biased to take advantage of that powerful chemistry.

10.5.B.vii. Disconnect from Atoms Bearing Certain Functional Groups. Certain functional groups are tied together along a reaction pathway. In many cases, the functional group transforms (CH–OH \rightarrow C=O and C=O \rightarrow CH–OH for example) involve ionic or polarized intermediates or reactants. Ionic functional group transformations are a useful illustration of this rule. Both anionic and cationic reactions involve a (positive) or (δ +) end, and a (negative) or (δ -) end. The functional groups corresponding to these reactive fragments have a special

reactivity relationship which can be exploited. When a bond is disconnected, identification of each end of the disconnect product as a donor or acceptor can lead to identification of possible reaction pathways to reconnect the bond (discussed in sec. 1.2). The disconnection of **101** with the appropriate



donor and acceptor sites clearly suggests an **aldol condensation** (sec. 9.4.A), where **101** can be synthesized from a synthetic equivalent of **102**.

The disconnection $103 \Rightarrow 104$ suggests a relationship between the tertiary amine in 103 and the dienyl azide moieties in 104.¹¹⁷ When 104 was heated in toluene, a [3+2]-cycloaddition occurred to give a triazoline (105) (sec. 11.11.H), but this unstable molecule decomposed (with loss of nitrogen) to form vinyl aziridine 106 as a mixture of stereoisomers.¹¹⁷ When 106 was heated to 480°C (using flash vacuum pyrolysis, FVP), the nitrogen analog of a vinylcyclopropane rearrangement (sec. 11.12.B) occurred, and the resulting product was subjected to catalytic hydrogenation to give 103. This reaction sequence (azide addition, vinylcyclopropane rearrangement) led to a bicyclic amine, linking the amine in 103 with the azido diene moieties in 104. Clearly, the special relationship of these groups is exploited by a combination of reactions.



^{117.} Hudlicky, T.; Seoane, G.; Lovelace, T.C. J. Org. Chem. 1988, 53, 2094.

10.5.B.viii. Consider Bonds Related by Known Transforms. Some functional groups are related by the reactions that transform one to the other. They may be as obvious as alcohol \rightarrow ketone. There are other transformations that connect or disconnect several bonds and/or functional groups at one time. The relationship is not always obvious, but its recognition can lead to great simplification of a target in one disconnection.

An important and useful example is the **oxy-Cope rearrangement** (see Example 17 in Table 10.1) in which the diene structure is related to the alkene-ketone functionality in the final product. Another example is the well known 1,3 elimination reaction known as the **Grob fragmentation** (sec. 2.9.E).¹¹⁸ In a synthesis of periplanone C by Saicic and co-workers,¹¹⁹ treatment of **107** with methanesulfonyl chloride generated the primary mesylate. Subsequent treatment with KOH led to the alkoxide and Grob fragmentation as shown gave **108** in 75% yield from **107**. In this case, the alkoxide and the leaving group (mesylate) are related to the carbonyl and alkenyl unit via the 1,3-elimination. Recognition of the spatial and structural relationships of the Grob fragmentation allows one to plan the disconnection, **108** \Rightarrow **106**.



10.6. STRATEGIC BONDS IN RINGS

10.6.A. Carbocyclic Rings

In addition to the eight criteria in Section 10.5.B, there is a ninth criterion⁷⁸ that identifies strategic bonds in rings. Bonds are strategic because their disconnection maximizes the simplification of a polycyclic molecule. Corey devised a set of guidelines that accommodate the special problems encountered in monocyclic and polycyclic structures.⁷²

- 1. Strategic bonds must be in a primary ring. A primary ring cannot be expressed
- as the envelope of two or more smaller rings bridged or fused to one another.^{72,120} Five-, six- and sevenmembered rings are usually easy to form, whereas other rings (especially C-8 and larger) are difficult to form by cyclization techniques (secs. 1.5.C, sec. 6.6.B). The two



^{118. (}a) Grob, C.A. *Experientia* **1957**, *13*, 126; (b) Cherbuliez, E. Baehler, Br.; Rabinowitz, J. *Helv. Chim. Acta* **1961**, *44*, 1820 (c) Zurflüh, R.; Wall, E.N.; Siddall, J.B.; Edwards, J.A. J. Am. Chem. Soc. **1968**, *90*, 6224.

^{119.} Ivkovic, A.; Matovic, R.; Saicic, R.N. Org. Lett. 2004, 6, 1221.

^{120.} See Reference 72, footnotes 8-10 cited therein.

six-membered rings A and B in **109AB** are primary rings, but the 10-membered ring C (see **109C**) that encloses A and B is not (i.e., bond *k* is *not* strategic). It is important to note that bonds *a-i* are all strategic by this rule since every one is a part of a primary ring. The presence of ring C as an envelope of rings A and B does not change this.

2. Strategic bonds must be directly attached to another ring. The strategic bond should be exo to another ring. A ring disconnection that produces two functionalized appendages leads to a more complex overall synthesis. Three disconnections are shown for 110. Paths I and II disconnect a bond exo to ring A to give 112 and 113, respectively. Synthetically, this ring-closure is straightforward, and may potentially proceed with stereoselectivity. Disconnection III leads to 111, which is a more difficult intermediate to prepare. Although the ring closure for III is probably facile, the disconnections in I or II lead to greater simplification and have a greater potential for stereocontrol. There are very few ring closure methods in which bonds are fused to preexisting three-membered rings and strategic bonds may not be exo to rings of that size.^{72,120}



3. Strategic bonds must be in rings with the greatest degree of bridging. Disconnection of a bond that is highly bridged (connected to several rings) leads to greater simplification of that structure. Disconnection A in the highly bridged four-membered ring of 114 leads to 115, with a bicyclo[4.4.0]decane unit, whereas disconnection B leads to 116. The bicyclo[3.1.1]heptane ring system in 116 is less accessible, and provides less simplification when compared to 115.



A maximum bridging ring is defined as one that is bridged at the greatest number of sites. The maximum bridging ring(s) is(are) selected from the set of "synthetically significant rings that is defined as the set of all primary rings and all secondary rings less than eight membered."^{72,120} Structure 117 has six significant rings: A, B, C, D, E, and F.¹²⁰ The highlighted rings in $A \rightarrow D$ are primary rings, but those in E and F are secondary. Ring structure C is bridged at four sites, more than any other, and is the maximal bridging ring.⁷² Ring B contains as many bridgehead sites as C, but it is not a maximal bridging ring, because it is bridged to other rings at only two of these sites

(b and d). Therefore, the number of times a ring is bridged is not a valid criterion for determining maximal bridging character. Ring E is bridged to as many rings as ring A but has one less bridgehead site than C.



4. Bonds common to a pair of bridged primary rings are not strategic. Any bond common to a *pair* of bridged or fused primary rings whose envelope is eight membered or larger cannot be strategic.⁷² Such a disconnection would generate a ring of more than seven members. Disconnection of the central bond in 109 would result in a 10-membered ring compound (118), and rings of this size are often

difficult to synthesize. For that reason, this type of <u>109</u> <u>118</u> disconnection should be avoided.¹²⁰ If the two fused or bridged rings are *directly* joined elsewhere by another bond (as in 114), the bond *may* be strategic. As shown in 114, disconnection of the indicated bond does not produce a 10-membered ring but two fused six-membered rings (see 115). Similar disconnection in 109, however, gives a 10-membered ring (118), as mentioned above, and is not strategic.

109

118



- **5.** Bonds within aromatic rings are not strategic. Aromatic nuclei are common fragments in natural products but they are usually incorporated as intact units of another fragment, although aromatic rings can be reduced and converted to other functionality. Although introduction of a phenyl ring and reduction (**Birch reduction**, see sec. 4.9.E) to a cyclohexadiene or cyclohexenone is common, incorporation of a cyclohexene and later oxidation to a phenyl ring is rare. Notable exceptions are quinones (sec. 3.3.A), which are commonly used as synthesis and later converted to functionalized aromatic rings.¹²¹ Incorporation of a carbocyclic ring and subsequent aromatization often requires harsh conditions and several synthetic steps. For these reasons, it is rarely useful to create an aromatic ring in a disconnection step unless aromatization is facile and non-injurious to other functionality.
- 6. In a cyclic arc, cleavage of the bond should not leave stereocenters in the side chain. Reactions that join two fragments to generate a chiral center allow greater

^{121. (}a) Fu, P.P.; Harvey, R.G. Chem. Rev. 1978, 78, 317; (b) Walker, D.; Hiebert, J.D. Ibid. 1967, 67, 153; (c) Jackman, L.M. Adv. Org. Chem. 1960, 2, 329.

control than those reactions that join fragments containing a chiral center remote to the site of bond formation. Disconnection of bond **B** in **119** would lead to **120**, requiring the synthesis of the alcohol with a stereogenic center on the chain prior to ring closure. It is not clear there would be any control over the stereochemistry of that center as it is formed. The reaction resulting from disconnection of bond **A** (to **121**), however, forms the ring and generates the stereogenic center simultaneously. Disconnection of **119** to **121** will lead to a shorter synthetic sequence, and there is the possibility that it can proceed with reasonable stereoselectivity.



A special case arises when the bond is attached to a stereogenic center, but that center is not the only one on the arc linking the two common atoms.⁷² Such a bond may be strategic. In **122**, bond *a* is strategic, since the arc in the disconnect product (**123**) does not contain an asymmetric center. In **124**, the arc contains a stereogenic center, and bond *a* is not strategic, since that disconnection gives **125**.



These rules can be applied to a carbocyclic molecule such as **126**. An analysis based on these six rules is shown in Table 10.2.⁷² Rule 1 shows that all bonds are part of a primary ring and rule 5 does not apply since there are no aromatic rings. Rule 2 shows that several bonds are exo to primary rings, indicated in **A**. The primary rings are highlighted in **B-D**. There are larger rings forming an envelope of these smaller rings, but bonds exo to those highlighted rings will take into account all possibilities. Rule 3 suggests that bonds *i*, *j*, *l*, *f*, and *n* are part of bridging rings. Disconnection of bond *m* is ruled out since the disconnection is away from the stereogenic center and does not involve an exo bond. Disconnection of bond *k* leads to a large ring and is ruled out. Bonds *b-d*, *f*, and *g-i* are not disconnected since it would violate Rule 6.

		$ \begin{array}{c} l \\ e \\ k \\ \lambda \\ b \end{array} $	$\int_{0}^{d} c$		ζ			B	C C								
			RU	LE ^a					RULE ^a								
BOND	1	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	STRATEGIC	BOND	1	<u>2</u>	<u>3</u>	<u>4</u>	<u>5</u>	<u>6</u>	STRATEGIC		
а		Y		Y	Х			h					Х				
b					Х			i		Y	Y		Х	Y	YES		
с					Х			j		Y	Y		Х	Y	YES		
d					Х			k		Y		Х	Х	Y			
e		Y			Х	Y		1		Y	Y		Х	Y	YES		
f		Y	Y		Х	Y	YES	m					Х				
g					Х			n		Y	Y		Х	Y	YES		
Y = rule ap	Y = rule applies, and $X =$ rule is not applicable.																

 Table 10.2.
 Strategic Bond Analysis for Carbocyclic Compound 126

10.6.B. Heterocyclic Rings

The six rules discussed in Section 10.6.A apply to many carbocyclic ring systems. If a bond in the ring is connected to an heteroatom, that bond can be considered strategic if it satisfies rules 2, 4, 5 and 6. Corey generated the strategic bonds for lycopodine (**127**) in Figure 10.6, using these rules.⁷² Bonds 3, 12, 14, and 19 were found to be strategic for the *first* disconnection. Thereafter, these bonds may or may not be strategic in the disconnect product, which should be reexamined to determine new strategic bonds. This process is continued as needed to generate a synthetic tree. The process used to determine strategic bonds in lycopodine followed five steps. (*I*) Structure of lycopodine (arbitrary bond numbering in **127**). (*2*) Primary rings. There are four primary rings, highlighted in **A-D**. (*3*) No synthetically significant (< eightmembered) secondary rings. (*4*) Bridgehead atoms. There are two, marked with (•) in **127**. (*5*) Strategic bond determination by the carbocyclic procedure.



Bond Number as in 127																			
Rule 1:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 2:			3	4	5	6		8	9	10		12		14	15	16			19
Rule 3:					5			8	9	10		12	13	14	15				
Rule 4:	1	2	3			6	7	8		10	11	12	13	14		16	17	18	19
Rule 5:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 6:	1	2	3	4	5	6	7		9		11	12	13	14	15	16	17	18	19
Strategic bond determination: carbon-heteroatom procedure																			
Bond Number																			
Rule 2b:			3	4															19
Rule 4:	1	2	3			6	7	8		10	11	12	13	14		16	17	18	19
Rule 5:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Rule 6:	1	2	3	4	5	6	7		9		11	12	13	14	15	16	17	18	19
The Strate	The Strategic bonds are: 3, 12, 14, 19 (see E)																		

Figure 10.6. Strategic bond analysis of lycopodine, **127**. [Reprinted with permission from Corey, E.J.; Howe, W.J.; Orf, H.W.; Pensak, D.A.; Petersson, G. J. Am. Chem. Soc. **1975**, 97, 6116. Copyright © 1975 American Chemical Society.]

Disconnection of bonds e and a leads to complex ring systems relative to the other disconnections, bonds l, n, f, j, and i. These fragmentations show reasonable simplification of the ring system and can be reformed by reasonable synthetic routes. Rule 4 (bridgehead atoms) discounts only bond k since it would open to a 10-membered ring, which leads to bonds l, f, n, j, and i as strategic (see the highlighted bonds in E).

A retrosynthetic analysis of Stork's synthesis of lycopodine is outlined in Scheme 10.9.¹²² The numbering system used in Corey's analysis (Figure 10.6) is retained, with bonds 3, 12, 14 and 19 being strategic. Bond 19 of **127** is disconnected to give **128**. It is noted that Corey's rules do not formally list manipulation of functional groups prior to disconnection of the target, but such flexibility is expected in any plan. Disconnection of **128** to **129** involves cleavage of bond 19, strategic by Corey's analysis, and the novel use of an aromatic ring as the equivalent of bonds 16-19. Further disconnection shows that bond 15 in **129** is now strategic, although it is not in **127**. This observation emphasizes that each disconnect product should be analyzed separately, in order to make full use of the strategic bond approach and maximize one's synthetic options. Bond 3, which is strategic in **127**, is disconnected to give **130**, and disconnection of bond 20 gives **131**. The final disconnection (to **132** and ethyl 3-oxobutanoate) disconnects bonds 8 and 10. These bonds are not strategic in **127**, but they are strategic in a molecule such as **131**.

Corey provided several additional analyses for a variety of polycyclic molecules (see Figure 10.7).⁷² The strategic bonds are shown in bold lines offering several disconnections for each target. Disconnection of each strategicbond will lead to a different synthetic approach (a different branch on the synthetic tree). Indeed, disconnection of one strategic bond can

^{122. (}a) Stork, G.; Kretchmer, R.A.; Schlessinger, R.H. J. Am. Chem. Soc. 1968, 90, 1647; (b) Stork, G., Pure Appl. Chem. 1968, 17, 383.

generate several completely different syntheses (see Section 10.7).



Scheme 10.9. Stork and co-worker's synthesis of lycopodine (127).



Figure 10.7. Strategic bonds in selected ring systems. [Reprinted with permission from Corey, E.J.; Howe, W.J.; Orf, H.W.; Pensak, D.A.; Petersson, G. J. Am. Chem. Soc. 1975, 97, 6116. Copyright © 1975 American Chemical Society.]

10.6.C. An Intramolecular Strategy

Deslongchamps developed a strategy¹³ that relies on an intramolecular approach using unsymmetrical molecules with a rigid conformation and a needed absolute configuration. In

a cyclization reaction, two ends of a molecule react and the transition state will assume many if not all of the conformational restrictions imposed by the ring being formed, as discussed in sections 1.5.B, 6.5, 6.6.B. This is a cyclization process, illustrated by the reactions $133 \rightarrow 134$, where X and Y are tied together by a chain of intervening methylene units. When compared with X+Y \rightarrow X-Y, there are more constraints on conformation and reactivity in 133. If two units of a cyclic molecule react, a polycyclic system is generated where reactivity



and stereochemistry are controlled by the rigid conformation of the cyclic precursor. This intramolecular reactions illustrated by $135 \rightarrow 136$. Indeed, there are more conformational

and reactivity constraints on 135 than on 133. It is possible to tie together a reaction center and a reagent, which will limit the angles from which a reagent can approach the reaction center with a great influence on the stereochemistry of the product.¹³ The chain length (n in 133) must allow generation of a ring with a low barrier to its formation (3-7, n = 1-5 in common5.B). Increasing chain rigidity by incorporating a cis double bond or a ring will increase the conformational restrictions on the reaction and will favor the cyclization process. Deslongchamps defined the conversion of 133 to 134 as a Level 1 Process (an intramolecular process having one chain).¹³ Compare this reaction with formation of 136 in which the reactive center and reagent in the precursor (135) are held together by tethering chains, and a higher degree of stereochemical control is observed. This transannular reaction is defined as a Level 2 Process (an intramolecular process with two chains).¹³ A synthetic plan based on a Level 2 process requires the use of medium and large rings. The ultimate degree of stereochemical restriction occurs when the reagent and substrate are held rigidly in space in an appropriate orientation for the desired reaction to take place.¹³

Scheme 10.10 outlines Deslongchamps' synthesis of triquinacene derivatives.¹²³ Manipulation of **Thiele's acid** (137) gave the key product, 138. A photochemical fragmentation gave 139, and an intramolecular aldol (sec. 9.4.A.ii) gave 140. With the basic skeleton formed, 140 was converted to triquinacene (141), and also to triquinacenecarboxylic acid (142). Scheme 10.10 provides an analysis of the synthesis, which involved a Level 1 intramolecular aldol (139 \rightarrow 140) and a reverse Level 1 process in the conversion of 138 \rightarrow 139.



Scheme 10.10. Deslongchamps' syntheses of triquinacene (141) and triquinacene carboxylic acid (142).

A synthesis involving a Level 2 process is Deslongchamps' synthesis of twistane (146), outlined in Scheme 10.11.¹²⁴ Treatment of 143 with sodium hydride in dioxane gave 144, and intramolecular displacement of the mesylate gave 4-twistanone, 145. The two reacting groups are brought into proper position by the transannular nature of the cyclization.

^{123.} Deslongchamps, P.; Cheriyan, U.O.; Lambert, Y.; Mercier, J.-C.; Ruest, L.; Russo, R.; Soucy, P. Can. J. Chem. 1978, 56, 1687.

^{124.} Gauthier, J.; Deslongchamps, P. Can. J. Chem. 1967, 45, 297.



Scheme 10.11. An outline of Deslongchamps' synthesis of twistane, 146.

10.7. SELECTED SYNTHETIC STRATEGIES: PANCRATISTATIN

As mentioned in Section 10.6.C, disconnection of a single strategic bond can lead to several different synthetic schemes. The nature of this approach maximizes individuality in a given synthesis and, as shown with lycopodine (127), many different strategies are possible. This diversity is shown explicitly by several syntheses of pancratistatin (13), first introduced in Section 10.2.A.

A few retrosynthetic analyses are illustrated in Schemes 10.12, 10.13, 10.14 and 10.15 of the several syntheses of **13** that appear in the literature.^{18e} In addition, Keck and co-workers synthesis of (+)-7-deoxypancratistatin $(172)^{125}$ is shown for a comparison of hat general

strategy. The four retrosyntheses for 13 shown in Schemes 10.12,¹²⁵ 10.13,¹²⁶ 10.14^{127} and 10.15,¹²⁸ respectively, are based on the actual published synthesis rather than a presynthesis analysis. A retrosynthesis for the closely related 7-deoxypancratistatin (172) is shown in Scheme 10.16.¹²⁹ An analysis of 13 via Corey's rules (sec. 10.6.A) suggests



that bonds 1, 2, 6, and 8 are strategic, with the amide bond 9 considered to be labile (see sec. 10.5.B.i). Bonds 13 and 14 could also be considered labile since they are part of an acetal unit.

^{125.} Keck, G.E.; McHardy, S.F.; Murry, J.A. J. Am. Chem. Soc, 1995, 117, 7289.

^{126. (}a) Iwao, M.; Reed, J.N.; Snieckus, V. J. Am. Chem. Soc. 1982, 104, 5531; (b) Watanabe, M.; Sahara, M.; Kubo, M.; Furukawa, S.; Billedeau, R.J.; Snieckus, V. J. Org. Chem. 1984, 49, 742.

^{127.} For example, see (a) Manitto, P. Biosynthesis of Natural Products, Halsted Press, John Wiley, New York, *1981*; (b) Steyn, P.S. (Ed.) The Biosynthesis of Mycotoxins. A Study in Secondary Metabolism, Academic Press, New York, *1980*; (c) Arigoni, D. Pure Appl. Chem. *1968*, *17*, 331; (d) Seiler, M.; Acklin, W.; Arigoni, D. J. Chem. Soc. D, *1970*, 1394; (e) Hamberg, M.; Swensson, J.; Wakabayaski, T.; Samuelsson, B. Proc. Natl. Acad. Sci. USA, *1974*, *71*, 345; (f) Hamberg, M. Samuelsson, B. J. Biol. Chem. *1967*, *242*, 5344.

^{128.} Stocking, E.M.; Williams, R.M. Angew. Chem. Int. Ed., 2003, 42, 3078.

 ⁽a) de la Torre, M.C.; Sierra, M.A. Angew. Chem. Int. Ed., 2004, 43, 160; (b) Johnson, W.S. Acc. Chem. Res. 1968, 1, 1; (c) Hendrickson, J.B., The Molecules of Nature W.A. Benjamin, New York, 1965, pp 12-57; (d) Bernfeld, P. Biogenesis of Natural Compounds, Pergamon Press, 1963.

In Scheme 10.12,¹²⁵ the first disconnection of Danishefsky's synthesis involved cleavage of bond 9 (the amide), converting the carboxyl unit to a lactone and the amine unit to a trichloroimidate. This disconnection also changed the trans stereochemistry found in **13** to the cis stereochemistry shown for **147**, allowing a Diels-Alder-based strategy that produced the cyclohexene ring in **148**. Disconnection to **149** mainly involved functional group manipulation that allowed the hydroxyl groups to be incorporated with the correct relative stereochemistry. This functional group manipulation was continued in the disconnection to **150**, which contained the requisite cyclohexene unit. constructed via a Diels-Alder reaction from diene disconnect product **151**, which disconnects bonds 4 and 6. This diene unit was prepared from aldehyde **152** via disconnection of bond 1. Disconnection of bond 10 in **152** as well as bond 1 led to pyrogallol (**153**) as the starting material. The actual synthesis involved a total of 26 steps that produced racemic **13**. It appears that the key disconnection was bond 9, the amide unit, bonds 4 and 6 for the Diels-Alder reaction, and bonds 1 and 10 for attachment of groups to the aromatic ring.



Scheme 10.12. Retrosynthetic analysis of Danishefsky's pancratistatin synthesis.

In Hudlicky's retrosynthetic analysis (Scheme 10.13),¹²⁶ bonds 9 and 1 were utilized. The amide bond (9) was again disconnected but to a *N*-Boc ester (**154**) rather than the lactone seen in Danishefsky's synthesis. Manipulation of the functional groups was also different, proceeding via the epoxide shown in **154**. Disconnection to **155** illustrates the manner in which the functional groups were manipulated, setting up disconnection of bond 1 to give two products, **156** and **157**. Amide **156** was prepared from commercially available materials, and

contains bonds 10-12. Fragment **157** contains one entire ring of **13**, and this differs significantly from Danishefsky's synthesis, where this ring was put together via a Diels-Alder reaction that required extensive manipulation (and steps) to obtain the desired functionality. In Hudlicky's approach, this ring is incorporated intact, and contains functionality that allows the tetraol unit to be incorporated more efficiently. The key step is the disconnection of **155** to **156** and **157**, where the two fragments were attached by an ortho-metalation procedure described by Snieckus and co-workers (see sec. 8.5.F).¹²⁶ Fragment **157** is derived from **158**, which is commercially available, but is generated by reaction of bromobenzene with *Pseudomonas putida*, as described in sec. 3.5.D. This synthesis produced (+)-pancratistatin, and required 16 steps from the commercially available diol **158**, and 17 steps if **158** was prepared from bromobenzene.



Scheme 10.13. Retrosynthetic analysis of Hudlicky's pancratistatin synthesis.

Trost used bonds 9 and 10 as well as 8 and 1 as outlined in Scheme 10.14.¹²⁷ The first disconnections involve functional group manipulation to set up the ring for the hydroxyl units as in **159**. The next disconnection is a key step in which bond 10 is disconnected to give **160**, rather than bond 9 in the other syntheses. This disconnection implies generation of an aryllithium from the bromide in **160** adding to the isocyanate group, generating the lactam and the requisite ring. The next disconnection to **161** gives the precursors to the isocyanate as well as the hydroxyl precursors, which sets up the next key disconnection to give fragments **162** and **163**. The precursor to Grignard reagent **162** was prepared using a literature procedure, and azide **163** was derived from the next disconnection to **164**, a diol readily available from benzoquinone in five steps. With **64** as the starting material, this synthesis produced (+)-pancratistatin in ~ 16 steps. The bromide precursor to **162** was prepared separately. Since **164** was prepared from benzoquinone, the true starting material, five more steps are added to bring the total to 21.


Scheme 10.14. Retrosynthetic analysis of Trost's synthesis of pancratistatin.

Rigby's synthetic plan is outlined in Scheme 10.15^{128} and used bonds 1 and 10. As in the previous synthesis, the first two disconnections involve manipulation of the hydroxyl groups, first a disconnection to give **165** and then to **166**. It is noted that these disconnections represent several steps and a change in the stereochemistry of the ring juncture stereochemistry, which is not shown. Disconnection of bond 1 in **166** to **167** is a key step that uses a photoaddition reaction to set that bond in the synthesis. Disconnection of bond 10 in **167** leads to two fragments, **168** and **170**. As with Trost's synthesis, bond 10 will be set via an isocyanate in **168**, this time via a Curtius rearrangement. Fragment **168** is disconnected to give **169** as one of the starting materials. The ring is used as an intact entity, with functional group manipulation to give the hydroxyl groups. Fragment **170** is derived from the commercially available 2,3-dihydroxybenzaldehyde (**171**). The conversion of **169** to **168** required six steps. Counting the coupling of **168** to **170** as one step, and using **169** as the starting material, the overall synthesis produced (+)-pancratistatin in 24 steps. The synthesis involved an enzymatic resolution using cholesterol esterase, in the sequence that converted **169** to **168**, to prepare optically active material.





Scheme 10.15. Retrosynthetic analysis of Rigby's synthesis of pancratistatin.

Although 7-deoxypancratistatin (172) is missing the phenolic OH unit relative to 13, it is interesting to compare Keck's strategy (Scheme 10.16)¹²⁹ for the construction of the phenanthridone skeleton (see Scheme 10.15) with the other four syntheses. The initial disconnection removed bond 9 to give 173 where the lactam unit was converted to a lactone unit and the amine unit is protected similar to the strategy used by Danishefsky. Bond 9 was actually converted to a trifluoroacetyl amide unit and the last step in the synthesis is the key lactone to lactam reorganization. The next disconnection removes bond 7, which was not strategic using analysis by Corey's rules, to give 174. This is a key disconnection because the six-membered ring was made in the synthesis by a radical cyclization process (see sec. 13.7). It also illustrates that bond 7 is not strategic in 13 or 172, but it is strategic in 173 because now it is part of a primary ring. Remember, each new disconnect product must be reexamined for strategic bonds. Disconnection of 174 to 175 essentially sets up the ring for manipulation of functional groups, and the functionality necessary for the radical cyclization. Disconnection to 176 is also required to set the functionality and this allows a key disconnection to 177, which utilizes formation of an aryllithium to attack the ester carbonyl of 177 leading to the reorganized aldehyde-ketone 176 in the synthesis. Disconnection of 177 breaks the labile ester bond to give fragment 178, which is prepared by known methods, and 179 that contains the carbons of the tetraol ring in 172 along with appropriate functionality. This precursor is derived from the available D-gulonolactone (180). This synthesis produced (+)-7-deoxypancratistatin in 20 steps.





Scheme 10.16. Retrosynthetic analysis of Keck's synthesis of 7-deoxypancratistatin.

The syntheses in schemes 10.12-10.16 rely on disconnection of the amide bond (9), essentially a functional group interchange, although it is clearly not that simple since either bonds 1 or 10 are also disconnected. The three key rings, the benzene ring, the lactam ring and the tetraol ring are also targeted. Although the disconnected bonds are similar, the strategies differ based on which of the three rings is key. In the syntheses of Danishefsky, Hudlicky and Keck, the lactam ring was formed close to the end or at the end of the synthesis. In these cases, the other two functionalized rings formed atropisomers that made formation of the lactam difficult. Steps were added and the sequences modified to get around this problem. In Rigby's synthesis, the lactam ring was formed in the middle of the synthesis by linking the aromatic ring to the tetraol ring by an amid linkage, with formation of the lactam ring by a photoaddition reaction. In Hudlicky and Trost's syntheses the aromatic ring was joined to the tetraol ring, in one case by an aryl anion opening of an aziridine and in the other by a $S_N 2'$ type addition of an aryl anion to a functionalized cyclohexene derivative. The carbonyl and amine units were intact, allowing the lactam ring to be formed. In the syntheses of Danishefsky and Keck, the lactam ring was formed by a lactone-to-lactam reorganization, where the lactone unit linked the aryl ring to the tetraol ring. In Danishefsky's synthesis, the tetraol ring was generated by a Diels-Alder reaction and functional group manipulation. In the syntheses of Hudlicky, Trost, and Rigby the tetraol ring was incorporated as an intact ring, from different precursors, requiring functional group manipulation. In Keck's synthesis, the tetraol ring was constructed by manipulating a carbohydrate precursor that contained all the requisite carbons and functionality (a chiral template driven synthesis-see sec. 10.9 for other examples of this strategy). The actual key bonds used to generate the carbon skeleton are actually very similar, but the strategies for making those bonds generated vastly different total syntheses. Which is best? All methods produce the target and all have their strengths. The most efficient route that produces the best yield of the target is obviously one of the more important considerations, but best is always relative to the needs of those asking the question.

10.8. BIOMIMETIC APPROACH TO RETROSYNTHESIS

In previous sections, a target was analyzed and the disconnection analysis led to reactive fragments. The disconnection process was continued until a suitable starting material was found. The actual synthesis followed the disconnection sequence to construct the molecule. If there was a bias in the retrosynthesis or the actual synthesis, it was usually due to the special interests of the chemist, recognition of an attractive substructure, or special knowledge of one area of organic chemistry.

There is an important alternative to the disconnection approach in which the retrosynthetic plan is biased to follow the known biosynthetic pathway for a particular target. In effect, the biosynthetic route becomes the synthetic tree, and appropriate reagents must be found to mimic the processes that Nature accomplishes with enzymes. Knowledge about formation of the molecule in Nature, how its functional groups interact and which bonds are cleaved with what reagents is usually gathered during the isolation and identification process. In many cases, intermediates of the biosynthetic pathway (also called the biogenetic pathway) for the formation of a natural product are known. Targeting those intermediates to generate the synthetic tree will effectively mimic the biosynthetic pathway and is referred to as a **biomimetic** or a **biosynthetic approach**. Although many biopathways have been determined,¹²⁷ the pathways are known, such as biosynthetic Diels-Alder reactions,¹²⁸ and can be used to develop a biomimetic strategy for total synthesis. This method offers an important alternative in synthetic planning, however. A number of reviews are available that describe this approach when applied to total synthesis.¹²⁹

10.8.A. Polyene Cyclization

A good example of this approach is the **Johnson polyene cyclization reaction**, or just **polyene cyclization**.^{82c,130,133} This polyene cyclization reaction was termed the **Stork-Eschenmoser hypothesis** by Johnson, named after the scientists who made the proposal. The biogenetic pathway for production of the steroid lanosterol from acetyl coenzyme A (acetyl Co-A) is shown in Figure 10.8.¹³¹ From this Figure it is clear that squalene is the direct biogenetic precursor of squalene-2,3-epoxide (**181**), which is the direct precursor to lanosterol. Lanosterol is ultimately converted to cholesterol,^{132,135} where enzymes close the ring in the biological process. The Stork-Eschenmoser hypothesis reasoned that treatment of a squalene-like polyene (all trans double bonds) with an appropriate acid would lead to a carbocation and the proximity

^{130.} Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, *2005*, pp. 348-349.

^{131. (}a) Clayton, R.B. Quart. Rev. Chem. Soc. 1965, 19, 168; (b) van Tamelen, E.E.; Willett, J.D.; Clayton, R.B.; Lord, K.E. J. Am. Chem. Soc. 1966, 88, 4752; (c) Corey, E.J.; Russey, W.E. Ortiz de Montellano, P.R. Ibid. 1966, 88, 4750; (d) Corey, E.J.; Russey, W.E. Ibid. 1966, 88, 4751.

^{132.} Wendt, K.U.; Schulz, G.E.; Corey, E.J.; Liu, D.R. Angew. Chem. Int. Ed., 2000, 39, 2812.

of the C=C units would lead to ring formation.¹³³ If this occurred in a sequential manner, several rings would be formed to build the polycyclic system via carbocation intermediates.¹³⁷



Figure 10.8. The biogenesis of cholesterol from acetyl coenzyme-A.

An all-chair conformation was assumed to be preferred for this polyene system, and an alltrans geometry was required for the double bonds to be in the proper position for cyclization to the proper stereochemistry. In work by Johnson and co-workers, addition of an acid catalyst to the terminal π bond generated a cation from **181**. Each π bond in turn acts as a nucleophile, and attacks the neighboring carbocation generated by the previous addition. Each ring closing reaction proceeds via a *six-center transition state*. In the final step, formation of a fivemembered ring should be favored and the process is terminated by an E1 reaction (sec. 2.9.B) to give **182**. If the alkene precursor has an (*E*) geometry, the cyclic product should be the more stable trans-fused ring due to the thermodynamic (equilibrium) nature of the cyclization, which was confirmed when treatment of trienes **183** and **185** with acid gave the same trans-fused decalin, **184**.¹³⁴ The cis-fused decalin was not observed in either case.



 ⁽a) Stork, G.; Burgstahler, A.W. J. Am. Chem. Soc. 1955, 77, 5068; (b) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. Helv. Chim. Acta 1955, 38, 1890.

^{134.} Stadler, P.A.; Nechvatal, A.; Frey, A.J.; Eschenmoser, A. Helv. Chim. Acta 1957, 40, 1373.



When this process was extended to tetraene (186),¹³⁵ treatment with acid gave the expected tricyclic alcohol (187), but in only 5-10% yield. The remainder of the product mixture was an intractable oil. As the number of rings being formed increased, the yield and efficiency of the polyene cyclization decreased. This problem was eventually solved by three synthetic modifications: (1) incorporation of one pre-formed ring into the polyene system to stabilize the conformation, (2) incorporation of a more reactive center at the terminus, and (3) use of a milder and more selective acid. The planned cyclization is a Level 1 intramolecular cyclization, as described by Deslongchamps (sec. 10.6.C).¹³ In acyclic systems, the conformation required for cyclization may not be the low energy conformation assumed by the polyene. When the polyene is attached to a preformed ring, the conformational stability of that ring must stabilize the entire polyene system in the lowest energy chair conformations required for efficient cyclization. Cyclopentanoid derivatives were found to be very effective. Once the cyclization process has begun, it is important to terminate the cationic process in an efficient manner that minimizes competitive side reactions. Incorporation of an alkyne or a vinyl fluoride at the reaction terminus will give a vinyl cation or an α -fluoro cation, respectively.¹³⁶ In both cases, the highly reactive cation product will trap a nucleophile in an S_N1 process, stopping the cyclization process. Finally, acids such as hydrofluoric acid and trifluoroacetic acid were found to be effective catalysts for the cyclization.¹³³ They are strong acids, but are not oxidizing acids, and the gegenions do not induce secondary reactions during the cyclization or termination steps.

This approach is shown in the synthesis of progesterone (193) in Scheme 10.17.¹³⁷ A Wittig olefination¹³⁸ (sec. 8.8.A) coupled **188** with **189**. The improved technology developed for the

^{135. (}a) Reference 133b, p 3 and reference 6 cited therein; (b) Eschenmoser, A.; Felix, D.; Gut, M.; Meier, J.; Stadler, P. in *CIBA Foundation Symposium on the Biosynthesis of Terpenes and Steroids*, Wolestenholme, G.E.W.; O'Connor, M. (Eds.), J and A Churchill Ltd., London, *1959*.

^{136. (}a) Johnson, W.S.; McCarry, B.E.; Markezich, R.L.; Boots, S.G. J. Am. Chem. Soc. 1980, 102, 352; (b) van Tamelen, E.E. Loughhead, D.G. Ibid. 1980, 102, 869; (c) Hoye, T.R.; Kurth, M.J. Ibid. 1979, 101, 5065.

^{137.} Johnson, W.S.; Gravestock, M.B.; McCarry, B.E. J. Am. Chem. Soc. 1971, 93, 4332.

 ^{138. (}a) Wittig, G.; Schöllkopf, U. Berichte 1954, 87, 1318; (b) Wittig, G.; Haag, W. Ibid. 1955, 88, 1654; (c) Trippett, S. Quart. Rev. Chem. Soc. 1963, 17, 406; (d) Wittig, G. Acc. Chem. Res. 1974, 7, 6.

cyclization led to a good yield of **192** from **191**. Polyene **191** was prepared by an intramolecular aldol condensation (sec. 9.4.A.ii) after hydrolysis of the dioxolane protecting groups in **190** (sec. 7.3.B.i).



Scheme 10.17. Johnson and Co-Worker's Synthesis of Progesterone.

Choice of reagents and reaction conditions are critical for success in polyene cyclizations. The exact cyclization conditions are often specific to the particular target. It is also clear that to accomplish chemically what enzymes do routinely presents many problems, often in the areas of regio- and stereocontrol. Only if these problems can be overcome by suitable choice of reagents and conditions, can a biogenetic route be used successfully. An enantioselective polyene cyclization usedg SnCl₄ mixed with BINOL derivatives¹³⁹ in which (–)-ambrox (**195**), the most important commercial substituent for ambergris used in the perfume industry, was prepared from triene **194**. Tricyclic compound **195** was obtained in 30% yield, but with only modest enantiopurity (42% ee). Three other tricyclic compounds were obtained as well (total yield of cyclized products was 54%). When the polyene was anchored to an aromatic ring, however, this approach gave good yields of polycyclic compounds with good enantioselectivity (62-87% ee).

$$\begin{array}{c} 2 \text{ equiv} & \overrightarrow{OH} & SnCl_4 \\ \hline & & & \\ \hline & & \\ 194 \end{array} & \overrightarrow{CH_2Cl_2, -78^\circ C, 3 \text{ days, 54\% yield}} & & \\ \end{array}$$

^{139.} Ishihara, K.; Nakamura, S.; Yamamoto, H. J. Am. Chem. Soc. 1999, 121, 4906.

10.8.B. Sparteine

van Tamelen and co-worker's synthesis of sparteine (201), outlined in Scheme 10.18,¹⁴⁰ is another example that follows a known biosynthetic pathway. In this case, conversion of diaminoketoaldehyde 198 to 8-ketosparteine (200) was the key biosynthetic step. van Tamelen did not use the labile and unavailable aminoaldehyde (198), but rather a synthetic equivalent of this compound. A synthetic equivalent is simply a molecule that is converted to the molecule of interest, or to a molecule that reacts identically and is later unmasked. The chemical structure of the synthetic equivalent may be different but the final product is the same. In this example, the synthetic equivalent of **198** is the bis(iminium) ketone **197**, generated from amino-ketone 196 by treatment with mercuric salts. van Tamelen's synthesis of sparteine (201) begins with piperidine. Generation of the synthetic equivalent 197 led to 199 and then 200 via sequential Mannich reactions. Wolff-Kishner reduction (sec. 4.10.A) of 200 gave 201. The Mannich **reaction**¹⁴¹ (secs. 9.7.A, 9.7.C) usually gives the thermodynamically more stable product via addition of an intermediate enolate (or enol) to an iminium salt ($H_2C=NMe_2^+$), which is produced in situ. When 2-methylcyclohexanone was treated with dimethylamine and formaldehyde, for example, both the kinetic product (203) and the thermodynamic product (202) were formed, with 202 predominating.



Scheme 10.18. van Tamelen and co-Worker's Synthesis of Sparteine (201).



^{140.} van Tamelen, E.E.; Foltz, R.L. J. Am. Chem. Soc. 1960, 82, 2400.

^{141. (}a) Blicke, F.F. Org. React. 1942, 1, 303; (b) Maxwell, C.E. Org. Syn. Coll. Vol. 3 1958, 305.

10.8.C. Deoxyerythronolide B

The final example illustrates yet another use of the biomimetic approach. Figure 10.9^{142} shows a retrosynthetic representation for Masamune's synthesis of deoxyerythronolide B (204). The biosynthetic building blocks of this and other macrolide antibiotics are known to be acetate and/or propionate units combined head-to-tail, as seen in 204.¹⁴³ The stereocenters in 204 are clearly shown in the acyclic (seco acid) form of the macrolide (206a). The specific biopathway is not utilized but rather modified to include the basic building blocks, seven propionate units (**bold lines** in **204**).¹⁴⁶ Seco acid **207** (X = OH) was constructed by sequential aldol condensation reactions (sec. 9.4.A) of propionaldehyde units, as shown by the disconnections in Figure 10.9. The chiral boron enolates derived from propanal control the symmetric induction. The diastereoface selectivity of the aldol condensation was discussed in Section 9.5.B.¹⁴⁴ Both (R) and (S) boron enolates of propional dehyde (**205a** and **205b**) were prepared and used as a fundamental biomimetic building block. Sequential aldol condensations generate the erythronolide skeleton, with the correct stereochemistry predominating in each aldol product. The targeted macrolide¹⁴⁶ was generated from the acyclic seco acid thioester (206b) via treatment with copper triflate and Hünig's base (diisopropylethyl amine). This and other techniques for macrolactonization¹⁴⁵ were discussed in Section 6.6.B.



^{142. (}a) Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. J. Am. Chem. Soc. 1981, 103, 1566; (b) Masamune, S.; Hirama, M.; Mori, S.; Ali, Sk.A.; Garvey, D.S. Ibid. 1981, 103, 1568 (c) Kaneda, T.; Butte, J.C.; Taubman, S.B.; Corcoran, J.W. J. Biol. Chem. 1962, 237, 322.

^{143. (}a) Birch, A.J.; Djerassi, C.; Dutcher, J.D.; Majer, J.; Perlman, D. Pride, E.; Rickards, R.W.; Thomson, P.J. J. Chem. Soc. 1964, 5274; (b) Manwaring, D.J.; Rickards, R.W.; Guadiano, G.; Nicolella, V. J. Antibiot., 1969, 22, 545; (c) Corcoran, J.W.; Chick, M. Biochemistry of the Macrolide Antibiotics, Ed. Snell, J.F. Academic Press, 1966, p 159;(d) Birch, A.J.; Pride, E.; Rickards, R.W.; Thomson, P.J.; Dutcher, J.D.; Perlman, D.; Djerassi. C. Chem. Ind., (London) 1960, 1245.

^{144. (}a) Evans, D.A.; Takacs, J.M.; McGee, L.R.; Ennis, M.D.; Mathre, D.J. Bartroli, J. *Pure Appl. Chem.* 1981, 53, 1109; (b) Evans, D.A.; McGee, L.R. *J. Am. Chem. Soc.* 1981, 103, 2876; (c) Evans, D.A.; Nelson, J.V.; Vogel, E.; Taber, T.R. *Ibid.* 1981, 103, 3099 and references cited therein; (d) Heathcock, C.H. *Science* 1981, 214, 395 and references cited therein.

^{145. (}a) Back, T.G. Tetrahedron 1977, 33, 3041; (b) Masamune, S.; Bates, G.S.; Corcoran, J.W. Angew. Chem. Int. Ed. 1977, 16, 585.



Figure 10.9. Retrosynthetic Analysis of the Seco Acid of Deoxyerythronolide B.

The synthetic examples in this section show that a biosynthetic pathway can be used to generate a synthetic tree, which can be of great utility and simplifies the task of growing the synthesis tree. If the biosynthesis is unknown one can turn to other processes for guidance.

10.9. THE CHIRAL TEMPLATE APPROACH

In the synthon approach,¹ a target was disconnected to give a suitable starting material, usually without prior knowledge of the identity of that compound. An alternative strategy generates strategic bond disconnections by "locating segments containing a number of chiral centers".¹⁴⁶ The fragments containing these stereogenic centers are part of a structure (a chiron, which is a chiral synthon), which will be a fragment of or related to a naturally occurring and/or readily available chiral material.¹⁴⁷ Such synthons are now commonly referred to as chiral templates. A chiral template is chosen by examination of the structure of a target for symmetry, chirality and functionality. This information is then *decoded* and transposed onto a carbon framework of a suitable synthetic precursor (the chiron or template). This has been called the chiron **approach**, but is more commonly referred to as the **chiral template approach**. The chiron is obtained from chiral starting materials (chiral templates) by systematic functionalization.^{151a} This process is illustrated in Figure 10.10,^{151a} where a target (**207**) is disconnected to a suitable chiron (208). The chiron is prepared from one of several chiral templates. Hanessian et al. analyzed a chiron-based synthesis in Figure 10.11,^{151a} in a general sense, and many of the elements found in Corey's various strategies are also found here. Hannessian also discusses the fundamental difference between Corey's synthon approach and the chiron approach. In Figure 10.12^{151a} the synthon approach was applied to a target, which was disconnected to a diene and a carbene.^{151a} The chiron disconnection led to a chiron (210) that is available from

146. Hanessian, S., Total Synthesis of Natural Products: The 'Chiron' Approach, Pergamon Press, 1983, p 22.

^{147. (}a) Hanessian, S.; Franco, J.; Larouche, B. Pure Appl. Chem. 1990, 62, 1887; (b) Reference 150, p 21.

a suitable chiral template (**209**).^{151a} The synthon approach can be correlated with "the type of functionality present in the target molecule and the chemical feasibility or precedent that dictates the strategy. The chiron approach to synthesis involves disconnection of strategic bonds in a target molecule, with minimal perturbation of stereogenic centers. A maximum overlap of functionality, as well as stereochemical and carbon framework relationships between target (or substructure) and the chiron is ideally sought. It is the type of substructure, and its possible chiral progenitor that dictate the strategy and chemistry to be carried out.¹⁴⁸



Figure 10.10. Model for total synthesis using the *chiron approach*. [Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.* **1990**, *62*, 1887. Copyright **1990** IUPAC.]



Figure 10.11. Anatomy of a synthesis using the *chiron approach*. [Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.* **1990**, *62*, 1887. Copyright **1990** IUPAC.]



Figure 10.12. A comparison of the *synthon approach* and the *chiron approach*. [Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.*, **1990**, 62, 1887. Copyright **1990** IUPAC.]

The distinguishing feature of the chiral template approach is recognition of the structural elements of a particular compound within the target structure. The retrosynthetic scheme is

^{148.} Reference 150, p 4.

then biased so that the selected molecule will be the starting material. This leads to a single branch of the synthesis tree rather than analysis of several branches.

There may be several chiral templates for a given chiron, so there is flexibility in the choice of which branch is chosen. This approach is analogous to Corey's starting material based strategy previously discussed in Section 10.4.⁶³ If the recognized starting material is readily available as a single enantiomer (see Figure 10.13),^{151a} the chirality of this compound can be transferred to the final target without a resolution step. This is clearly of great value and the main driving force for exploitation of this technique. Carbohydrates, amino acids or terpenes are a few of the many classes of organic compounds that provide readily available chiral molecules, usually from natural sources sometimes called the **chiral pool**. A few of these chiral starting materials are shown in Figure 10.13,^{151a} where they were used for the synthesis of naturally occurring molecules. It is important to note that the chiral template can be well hidden, as shown in Figures 10.13 and 10.14.^{151a} (*S*)-Carvone was the chiral template for a disconnection analysis of eucannabinolide (**211**), and (+)-camphor was the chiral template for pheromone **212**.^{151a} Some searching is required to discover the 'hiding place' of these chiral templates in the target (see Figure 10.14).



Partially hidden chiral templates in punctatin A, α -kainic acid, forskolin and an amino acid from pepstatin



Figure 10.13. Hidden chiral templates. [Reprinted from Hanessian, S.; Franco, J.; Larouche, B. Pure. Appl. Chem., 1990, 62, 1887. Copyright 1990 IUPAC.]



Figure 10.14. Very hidden chiral templates. [Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.*, **1990**, *62*, 1887. Copyright **1990** IUPAC.]

In general, Hanessian discusses three types of asymmetric induction that are pertinent to all syntheses, not only those to which the chiron approach will be applied (see Figure 10.15).^{151a} The first type of asymmetric induction is auxiliary dependent (a chiral auxiliary is attached to an achiral substrate, used to transfer asymmetry during the reaction and later removed). The internal (resident chirality) dependent form of asymmetric induction relies on a chiral center being part of the reactant. The external type of asymmetric induction makes use of a chiral reagent or a chiral catalyst. Auxiliaries were used in Chapter 9 for asymmetric aldol condensations (sec. 9.5). Internal asymmetric induction was a key element of Cram's rule as applied to reductions (sec. 4.7.B) and Grignard addition to carbonyl derivatives (sec. 8.4.F.ii), as well as stereodifferentiation reactions related to the **aldol condensation** (see. 8.7.A), in asymmetric Grignard reagents (sec. 8.4.F.), and in organocuprate reactions (sec. 8.7.A.vii).



Figure 10.15. Types of asymmetric induction. [Reprinted from Hanessian, S.; Franco, J.; Larouche, B. *Pure. Appl. Chem.*, **1990**, *62*, 1887. Copyright **1990** IUPAC.]

Carbohydrates are particularly useful chiral templates.¹⁴⁹ The pyranose or furanose form of a sugar can be opened to give a chiral acyclic fragment. Functional groups can be systematically replaced with others, with a high degree of stereocontrol. In Figure 10.16¹⁵⁰ an analysis of erythronolide A (**213**) reveals two carbohydrate chirons, **214** and **215**. Various synthetic manipulations of the sugar moiety are also shown, eventually leading to a recognizable sugar (D-glucose) protected as the *O*-methyl derivative.

Fraser-Reid suggested that the two most valuable advantages offered by carbohydrate derivatives for organic synthesis are (I) highly stereoselective reactions resulting from conformational bias and (2) ready proof of molecular stereochemistry.¹⁵¹ Synthetic targets with two to four

^{149.} Hanessian, S. Acc. Chem. Res. 1979, 12, 159.

^{150.} Reference 150, p 34.

^{151.} Anderson, R.C.; Fraser-Reid, B. J. Am. Chem. Soc. 1975, 97, 3870.

contiguous chiral centers can be constructed from chiral pyranose derivatives. Higher carbon sugars (with greater than four chiral centers) offer formidable challenges.^{152,153} Many macrolides, or segments thereof, may be regarded as higher carbohydrate sugars,¹⁵⁴ but challenges arise in stereoselectivity and availability in known configurations. Fraser-Reid outlined a concept termed **pyranoside homologation** to fill this need.^{155,156} The monograph by Hanessian provides an excellent description of this approach, using carbohydrates and many other chiral starting materials.¹⁵⁰ This monograph is strongly recommended to provide a detailed explanation of this approach. In this section, the approach can only be outlined in the context of beginning the construction of a synthetic tree based on the chiral template approach.



Figure 10.16. Chiron analysis of erythronolide A (**213**). [Reprinted from Hanessian, S., *Total Synthesis of Natural Products: The Chiron Approach*, Pergamon Press, **1983**, p. 34 by courtesy of Professor Stephen Hannesian. Copyright 1983, with permission from Elsevier Science]

Takahashi and Nakata's retrosynthesis of mucocin (216) in Scheme 10.19¹⁵⁷ clearly shows the disconnection roadmap has been biased toward three carbohydrates, D-galactose (221), 2,5-anhydro-D-mannitol (222) or L-rhamnose (224). Initial disconnection to two fragments (217 and 218) shows the convergent nature of the synthesis. Fragment 217 is disconnected to give two fragments, 219 and 220, and these fragments are derived from two of the sugar

152. Fraser-Reid, B.; Magdzinski, L.; Molino, B.F.; Mootoo, D.R. J. Org. Chem. 1987, 52, 4495.

154. Celmer, W.D. Pure Appl. Chem. 1971, 28, 413.

- 156. Fraser-Reid, B.; Magdzinski, L.; Molino, B. J. Am. Chem. Soc. 1984, 106, 731.
- 157. Takahashi, S.; Nakata, T. J. Org. Chem. 2002, 67, 5739.

^{153. (}a) Secrist, J.A.; Wu, S.-R. J. Org. Chem. 1979, 44, 1434; (b) Secrist III, J.A.; Barnes, K.D. Ibid. 1980, 45, 4526; (c) Brimacombe, J.S.; Kabir, A.K.M.S. Carbohydr. Res. 1986, 152, 329, 335; (d) Danishefsky, S.J.; Larson, E.; Springer, J.P. J. Am. Chem. Soc. 1985, 107, 1274.

^{155. (}a) Molino, B.F.; Magdzinski, L.; Fraser-Reid, B. *Tetrahedron Lett.* 1983, 24, 5819; (b) Magdzinski, L.; Cweiber, B.; Fraser-Reid, B. *Ibid.* 1983, 24, 5823; (c) Fraser-Reid, B.; Magdzinski, L.; Molino, B. in *Current Trends in Organic Synthesis*, Nozaki, H. (Ed.), Pergamon, New York, 1983.

precursors. Fragment **218** is derived from **223** by a series of steps, and this key fragment (**223**) is prepared from rhamnose. In the actual synthesis, significant functional group modification was required to convert each sugar into the appropriate synthetic fragment, which is both the major advantage and the major disadvantage of the method. It is a disadvantage in that the chiron approach does not necessarily lead to shorter syntheses, since the synthetic tree is pruned to give a single option. Persistence in a single approach may add several extra steps in functional group transformations. It may also lead to more difficult carbon-carbon bond forming reactions. There is usually sufficient pliability in the synthetic tree, however, that a reasonable pathway can be found that will accommodate an available chiral template without undue cost in time or synthetic difficulties. The advantage is that the asymmetry in the starting materials leads to increased enantioselectivity in all reactions, which usually means that no resolution steps are necessary.



Scheme 10.19. Chiral template-based retrosynthesis of mucocin (**216**). [Reprinted with permission from Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739, Copyright 2002, with permission from the American Chemical Society.]

Any chiral molecule available in Nature or other sources can, in principle, be used in a synthesis. Scheme 10.20^{158} shows Srikrishna's synthesis of (–)-neopupukean-10-one (**229**) from the chiral template (*R*)-carvone (**225**). Formation of the enolate anion at C6 and 1,4-addition to the conjugated ester, followed by a second conjugate addition of the resulting anion to the conjugated ketone at C3 leads to **226** after saponification of the ester. Formation of the acid chloride and reaction with diazomethane gave diazoketone **227**, and rhodium catalyzed insertion (see sec. 13.9.C.iii) closed the five-membered ring, and hydrogenation of the alkene unit gave **228**. Conversion of the less hindered ketone to the dithiolane and reductive cleavage with Raney nickel gave the target **229**. The carbon atoms in the template (**225**) are numbered in **226** and in **229** for convenience.

^{158.} Srikrishna, A.; Gharpure, S.J. Chem. Commun. 1998, 1589.



Scheme 10.20. Srikrishna and Gharpure's synthesis of (-)-neopupukean-10-one (229).

Hanessian and co-workers developed a computer program that will execute retrosynthetic plans based on the chiron approach, called **CHIRON**.¹⁵⁹ Hanessian synthesized (+)-meroquinene based on the analysis shown in Figure 10.17,^{163c} where the computer generated four chiral templates along with notations as to how they must be modified for conversion to a requisite chiron. In the total synthesis, tetraacetyl glucose was chosen as the chiral template starting material, readily available from D-glucose.¹⁶⁰ In a chiral template approach, not all of the chiral centers must be used. It is possible to use only one or two without changing the target, while other chiral centers are generated by highly diastereoselective and/or enantioselective reactions.



Figure 10.17. CHIRON analysis of meroquinene. [Reprinted with permission from Hanessian, S.; Faucher, A.-M.; Léger, S. *Tetrahedron* **1990**, *46*, 231, Copyright 1990, with permission from Elsevier Science.]

^{159. (}a) Reference 150, pp 9-22; (b) Hanessian, S.; Franco, J.; Gagnon, G.; Laramée, D.; Larouche, B. J. Chem. Int. Compt. Sci, 1990; 30, 413; (c) Hanessian, S.; Faucher, A.-M.; Léger, S. Tetrahedron 1990, 46, 231; (d) Hanessian, S.; Sakito, Y.; Dhanoa, D.; Baptistella, L. Ibid.. 1989, 45, 6623.

^{160.} Rao, D.R.; Lerner, L. Carbohydr. Res. 1972, 22, 345.

10.10. COMPUTER GENERATED STRATEGIES

In Section 10.4.B a computer based method for generating retrosyntheses was presented called LHASA, and Section 10.9 mentioned the computer program CHIRON. Computer methods are generically known as computer-assisted organic synthesis. This section will present two such approaches, the SYNGEN approach of Hendrickson, and the MARSEIL-SOS approach of Barone. Later generation programs are also available¹⁶¹ but this section will use the initially reported programs to introduce the fundamental approach.

10.10.A. Hendrickson's SYNGEN Approach

The strategic bond approach often leads to consecutive type syntheses, although disconnection of two or more strategic bonds can easily generate convergent pieces. The strategic bond approach generates intermediates on the synthetic tree in an interactive manner that leaves selection to the chemist.¹⁶² The interactive-decision making aspects of the strategic bond approach maximizes opportunities to create new methodology and strategy. If the aim, as stated by Deslongchamps,¹³ is to develop new methodology and chemistry as a lasting achievement then this is an attractive approach. If direct synthesis of a specific target by the most efficient route is more important than one that develops new methodology, then alternative strategies may be desirable. The interactive approach tends to focus on the first levels of the synthetic tree and does not allow the chemist to see which retrosynthetic start leads to early discovery of starting materials and so the shortest pathway.¹⁶⁶

Hendrickson pointed out that the stepwise backward protocol described in the previous sections suffers from several problems:¹⁶³ (1) The procedure creates too many intermediates to manage and most must be deleted without knowing if they will lead to more efficient syntheses. (2) There is no method for predicting yield. (3) The procedure requires an extensive database of transforms and reactions. (4) The focus of a transform is on the functional groups and those reactions that will completely remove a functional group are not discernible by this method. Estrone (232), for example, is easily obtained from 230 via stepwise reduction.^{164,165} Initial reduction of 230 gives 231, which was converted to 232. This sequence is not likely to be

^{161.} Ihlenfeldt, W.-D.; Gasteiger, J. Angew. Chem. Int. Ed. 1995, 34, 2613.

^{162.} Hendrickson, J.B. Acc. Chem. Res. 1986, 19, 274.

 ⁽a) Hendrickson, J.B.; Berstein, Z.; Miller, T.M.; Parks, C.; Toczko, A.G. Chapter 6 in ACS Symposium Series, No. 408, Hohne, B.; Pierce, T. (Eds.), American Chemical Society, Washington, DC, *1989*, pp 62-81; (b) Hendrickson, J.B. J. Chem. Inf. Compt. Sci. 1979, 19, 129.

^{164.} Ananchenko, S.N.; Torgov, I.V. Tetrahedron Lett. 1963, 1553.

^{165. (}a) Smith, H.; Hughes, G.A.; McLoughlin, B.J. *Experientia* 1963, 19, 177; (b) Smith, H.; Hughes, G.A.; Douglas, G.H.; Hartley, D.; McLoughlin, B.J.; Siddall, J.B.; Wendt, G.R.; Buzby, Jr., G.C.; Herbst, D.R.; Ledig, K.W.; McMenamin, J.R.; Pattison, T.W.; Suida, J.; Tokolics, J.; Edgren, R.A.; Jansen, A.B.A.; Gadsby, B.; Watson, D.H.R.; Phillips, P.C. *Ibid.* 1963, 11, 394; (c) Douglas, G.H.; Graves, J.M.H.; Hartley, D.; Hughes, G.A. McLoughin, B.J.; Siddall, J.; Smith, H. J. Chem. Soc. 1963, 5072.

derived from LHASA or the strategic bond approach since there are no functional groups that could be correlated with the pertinent transforms.



In a complex synthetic tree (see Figure 10.18),¹⁶⁶ which pathway is the best? As stated by Hendrickson, "selection, not generation, is the central problem."¹⁶⁷ The tree must be simplified and then subdivided. Assume that the retrosynthesis to a given target has five levels (five disconnect products). One disconnection may generate 30 reactions that can synthesize the target. If each of the disconnect targets is just as complex, the second disconnection will also generate ~ 30 reactions. If the synthesis is taken to five levels in the synthesis tree, each with the same 30-reaction complexity, there are 30^5 (24.3 million) routes.¹⁶⁷ If the reaction sequence has 25 steps, an already unmanageable problem becomes worse. If the number of synthetic routes at each disconnection stage were only three, a 25-step synthesis would have 25^3 (15,625) possibilities, still rather unmanageable. Hendrickson reported of four methods to simplify the synthesis tree:¹⁷⁰ (1) Systematize structures and reactions into digital form for a computer. (2) Simplify the tree by "condensing trivial disconnections into familial generalizations". (3) Subdivide the tree into independent subtrees that have no reactions in common, and analyze each subtree separately. (4) Select the optimal pathways.



Figure 10.18. The synthesis tree. [Reprinted with permission from Hendrickson, J.B. Acc. Chem. Res. **1986**, 19, 274. Copyright © 1986 American Chemical Society.]

^{166.} Hendrickson, J.R. J. Am. Chem. Soc. 1977, 99, 5439.

The process begins with a search for key reactions, the construction reactions (carbon-carbon bond-forming reactions) that will assemble the target skeleton from the skeletons of the starting materials. Initial consideration affords only a major simplification of the total synthesis tree to generate a construction tree. The construction tree contains only the key constructions that assemble the target skeleton from starting skeletons.¹⁶⁶ Each full synthetic sequence is a separate construction plan,¹⁶⁶ separated by the dashed lines in Figure 10.18, and each plan is an independent smaller tree that may be examined separately for its detailed chemistry.¹⁶⁶ This is systematized by breaking the target into smaller fragments. The simplest gross definition of a particular synthesis is the **bondset**-the set of all bonds constructed in a synthesis (γ in number).¹⁶⁷ The concept of bondset is illustrated by three different disconnection schemes¹⁷¹ for the same steroid: **233A** ($\gamma = 3$),¹⁶⁸ **233B** ($\gamma = 6$),¹⁶⁹ and **233C** ($\gamma = 8$).¹⁷⁰



[Reprinted with permission from Hendrickson, J.B. Accounts Chem. Res. 1986, 19, 274. Copyright © 1986 American Chemical Society.]

Such a bondset, once defined, implies a multistep sequence passing through the tree from starting material to target, seeing both at once.¹⁷¹ The bondset is a skeletal conception and immediately defines the skeleton of the starting material as well as the sites on each synthon at which construction is to occur (heavy dots), that is, the construction sites.¹⁷¹ Each bondset defines an independent subtree of synthetic sequences, all of which construct only that particular set of γ bonds in the target. In general, there are 8! ordered bondsets for a given molecule, although relatively few are efficient. Hendrickson's analysis indicated that the typical total synthesis constructs 25-33% of all skeletal bonds in the target using starting skeletal fragments averaging about three-to-four carbons. That is, for every three or four bonds that are made in

170. Reference 172, p 130.

 ⁽a) Hendrickson, J.B. Topics in Current Chemistry, 1976, 62, 51 (b) Hendrickson, J.B. J. Am. Chem. Soc. 1975, 97, 5763.

^{168.} Anand, N.; Bindra, J.S.; Ranganathan, S. Art in Organic Synthesis, Holden Day, 1970, p 181.

^{169.} Reference 172, pp 3,4.

⁽a) Velluz, L.; Nominé, G.; Amiard, G.; Torelli, V.; Cérède, J. *C.R. Hebd. Seances Acad. Sci.* 1963, 257, 3086;
(b) Velluz, L. Nominé, G.; Mathieu, J.; Toromanoff, E.; Bertin, D.; Vignau, M. Tessier, J. *Ibid.* 1960, 250, 1510;
(c) Velluz, L.; Nominé, G. Mathieu, J.; Toromanoff, E.; Bertin, D.; Tessier, J.; Pierdet, A. *Ibid.* 1960, 250, 1084.

a synthesis only one skeletal bond is made. Synthons actually used are predominantly acyclic unbranched skeletons of four carbons or less, or aromatic derivatives. The average size of starting materials can be defined as n_0/k for an overall average of 4.0 carbons. The bondset size as a proportion of the total bonds is therefore $\gamma/b_0 \approx 0.24$ (the construction ratio).

Hendrickson used two different syntheses of estrone (**232**) to illustrate this approach and Figure 10.19¹⁷¹ shows the bondsets, construction plans, and weights (see below) for both. Velluz and co-worker's convergent retrosynthetic strategy is shown in Figure 10.20^{58,171} and compred with the closely related syntheses of Torgov and Ananchenko¹⁶⁸ and Smith et al.¹⁶⁹ With Hendrickson's bondset analysis, the 18 carbons of **232** should give an average of six pieces, each of three or more carbons. If a molecule is composed of 15-25 carbons and the construction ratio of ≈ 0.21 , a synthesis should require 4-7 constructions.¹⁷¹ For this example, there are nine bond constructions ($\gamma = 9$). A skeleton of *n* atoms and *r* rings has $n_0 + r_0 - 1$ bonds and $b_0 = n_0 + r_0 - 1$. If there are *k* pieces then $\gamma = k + r_0 - r - 1$. The following definitions apply: b_0 = number of C-C single (σ) bonds in the target; n_0 = number of carbons in the target; r_0 = number of carbocyclic rings in the target; r = number of carbocyclic rings in the starting material; k = number of synthons; γ = number of bonds constructed (bondsets). For Velluz's synthesis, $b_0 = 21$, $n_0 = 18$, $r_0 = 4$, r = 0 and k = 6. Therefore, $b_0 = 18 + 4 - 1 = 21$ and $\gamma = 6 + 4 - 0 - 1 = 9$.



Figure 10.19. Bondsets and Construction Plans for Estrone (232). [Reprinted with permission from Hendrickson, J.B. J. Am. Chem. Soc. 1975, 97, 5763. Copyright © 1975 American Chemical Society.]



Figure 10.20. A convergent retrosynthetic analysis of Velluz's estrone synthesis. Total synthesis of estradiol, schematic. The figures between the individual stages indicate the numbers of reaction steps. (*) denotes optical resolution at that step. [Reproduced with permission from Velluz, L.; Valls, J.; Mathieu, J. *Angew. Chem. Int. Ed.* **1967**, *6*, 778. Copyright 1967 VCH Weinheim.]

Convergent syntheses disconnect the target into at least two pieces, each of which is further disconnected, which usually leads to a more efficient strategy as with the Torgov-Smith approach. Rather than proceeding backwards one step at a time, the convergent disconnection goes down many levels into the tree, closer to the starting materials to be used. After restricting the disconnection to the convergent type to maximize simplification, the next step is to examine the various functional groups and reactions necessary for the construction sequences. The number of steps should be kept to a minimum. In the estrone synthesis, there are 24 bonds. If these are to be made from one-carbon pieces (the bondset = 1), there are 24! (= 6 x 10²³ different pathways for assembly). The convergent strategy will increase the number of bondsets and decrease the number of convergent routes that can be applied.¹⁶⁷ If the bondset is increased to five members ($\gamma = 5$), there are 20,349 ways to cut estrone, but there are γ ! routes (2.5 million ordered bondsets), which is an enormous number, but better than 6 x 10²³.

Hendrickson devised a weighting scheme for each construction tree based on the weights of the several starting materials for each level of the synthesis tree.^{166,170} The fundamental idea is to calculate the overall weight of starting materials that will be required to generate a gram of the target. Since these molecular weights are unknown at the time the synthetic fragments are assembled, the number of skeletal carbons in each piece (η_i) and the weight sum (W) gives a measure of the efficiency of the reaction. The reciprocal of the average yield for each step is X, and the number of steps each fragment (i) passes through is l (the level of the starting material in the synthetic tree is i). The quantity W is then given by the expression¹⁶⁷

$$W = (\Sigma \eta_i)(X^{li})$$

Hendrickson provided a table of X^{li} values that are correlated to the number of steps (*l*, see Figure 10.21).¹⁶⁷ Table 10.3¹⁶⁷ reproduces Hendrickson's table, but the yield has been inserted, remembering that X is the *reciprocal* of the yield. The value of *W* assumes *no* refunctionalization in the synthesis.



Figure 10.21. Weighting scheme for synthetic tree analyses.

Table 10.3. Values of X^a and the Yield for Syntheses of Steps l

	X ¹	X ¹			X ¹	X ¹		
<u> / (No. Steps)</u>	<u>Approximate^a</u>	<u>Actual^a</u>	<u>% Yield</u>	<u>l (No. Steps)</u>	<u>Approximate^a</u>	<u>Actual^a</u>	<u>% Yield</u>	
1	1.25	1.25	80	9	7.5	7.45	13.4	
2	1.5	1.56	64.1	10	9.5	9.31	10.7	
3	2	1.95	51.3	11	11.5	11.64	8.6	$a X = \frac{1}{1}$
4	2.5	2.44	41.0	12	14.5	14.55	6.9	% yield
5	3	3.05	32.8	13	18	18.19	5.5	
6	4	3.81	26.2	14	23	22.7	4.4	
7	5	4.77	21.0	15	28	28.4	3.5	
8	6	5.96	16.8					

A simple analysis of **234** shows a three-level synthetic tree. The first disconnection (l = 1) to **235** (η = number of carbons = 11) and **236** (η = 5) requires a Diels-Alder disconnection (sec. 11.4.A). The level 2 disconnection to **237** (η = 7) and **238** (η = 4) is also a Diels-Alder disconnection. The final disconnection (level 3) generates cyclopentanone (**239**, η = 5) suggesting a condensation reaction with an organometallic. For this example, the weighted average (*W*) is given by the following calculation:



The weighted averages shown in Figures 10.21 and 10.19 were calculated in this manner. In Figure 10.21, synthesis tree II is taken to be the most efficient (lowest W) and represents the

fully convergent synthesis.

An ideal synthesis in the context of this method requires only sequential construction reactions, with no refunctionalization needed to repair functional groups between constructions.¹⁶⁶ This ideal synthesis was assumed in the weighting scheme discussed above, although it is very difficult to attain as a practical matter. Hendrickson's approach was to develop a numerical description of functionality.¹⁷² The structures become a list of simple numbers, ordered by the numbering of the skeletal carbons. A reaction is expressed by its net structural change, the arithmetic change in the functionality from substrate to product or vice versa.¹⁶⁶ The reaction is represented by a number list for the pertinent carbons that generate the substituent functionality when added to the product list (or *vice versa*).¹⁷³ Hendrickson chose to use half-reactions in the actual analysis,¹⁶⁶ and a construction reaction may be seen as two linked half-reactions on each side of the bond-formed.^{174,175} Each partial synthon undergoes a half-reaction and each construction half-reaction is characterized by the net structural change relating substrate and product for that particular synthon.¹⁶⁶ The skeletal format for construction of a half-reaction is characterized by the net structural change relating substrate and product (**241**). Functionality appears on

these carbons and changes from substrate to product in a manner characteristic of a given half-reaction.^{167b} A numerical system was developed to describe structures,^{156,158} based on four kinds of attachments to any carbon: to hydrogen (H); a σ bond (R); a π bond (II); and a carbon-heteroatom bond (Z). The functionality is then $\pi + z$ for a given skeleton of known σ bonds and <u>h</u> derived by difference. Functionality is, therefore, expressed by z and π .

These concepts led to the computer program **SYNGEN**¹⁶⁷ (**SYN**thesis **GEN**eration).^{176,177} As with Corey's LHASA program, inspection of the main principles of the program can offer useful information for a synthesis. It is emphasized that this section has only touched the surface of Hendrickson's detailed and comprehensive analysis. Once understood, any target can be analyzed in detail to provide a synthetic tree. The purpose of this discussion is to give general concepts that may be applied without a computer analysis or dependence on any one approach. With this in mind, SYNGEN has two parts. The first is a skeletal dissection of the target and the second is generation of functionality necessary to assemble the synthesis. There are several general rules for design of an optimal synthesis, as described by Hendrickson:¹⁶⁷

- 1. Minimize refunctionalization.
- 2. Refunctionalize early.

- 176. Hendrickson, J.B.; Braun-Keller, E.; Toczko, A.G. Tetrahedron (Suppl.) 1981, 37, 359.
- 177. Hendrickson, J.B. CHEMTECH 1998, 28(9), 35.

^{172. (}a)Hendrickson, J.B.J. Am. Chem. Soc. 1971, 93, 6847, 6854; (b)Hendrickson, J.B.J. Chem. Educ. 1978, 55, 216.

^{173.} For retrieval of reactions from databases, see Hendrickson, J.B.; Miller, T.M. J. Org. Chem. 1992, 57, 988.

^{174.} Hendrickson, J.B.; Grier, D.L.; Toczko, A.G. J. Am. Chem. Soc. 1985, 107, 5228.

^{175.} For a description of reactions, see Hendrickson, J.B. Recl. Trav. Chim. Bay-Bas 1992, 111, 323.

- 3. Minimize constructions (γ), which implies the use of large structural pieces of several constructions in a single step (sec. 10.5.B.vi for powerful reactions).
- 4. Join large pieces last to minimize their large weight loss.
- 5. Fully convergent routes are preferred.
- 6. Cyclize early. The structure weight will be minimized if cyclizations are carried out early.
- 7. Chiral resolution should come early. Since resolution discards > 50% of the material, the rationale is obvious.

There are nine characteristics of the SYNGEN approach.¹⁸⁰

- 1. It is an executive program not interactive with the chemist.
- 2. It assesses all possible routes within clearly defined constraints.
- 3. It uses digital expressions for molecules and reactions.
- 4. It dissects the initial skeleton for efficient assembly.
- 5. It draws on a pool of several thousand available starting materials .
- 6. It attempts to weight each route to economize the number of steps.
- 7. It limits the analysis primarily to construction reactions.
- 8. It generates reactions from mechanistic logic.
- 9. It does not predict yields.

Hendrickson summarized seven reductive criteria for the basic protocol of the approach.¹⁷⁸

- 1. Select from the target structure prime bonds for construction.
 - (a) Functionality criteria: pairwise consideration of functionality and their relative positions on the skeleton.
 - (b) Skeletal (and stereochemical) criteria.
- 2. Combine these bonds into bondsets, adequate to dissect reasonable synthon skeletons but minimal in γ .
- 3. From each bondset isolate the synthon skeletons dissected, noting the pattern of construction sites on each.
- 4. For each synthon skeleton, locate in the general sequence list corresponding to its pattern of construction sites the sequences applicable to the skeletal (σ) levels of those sites. This defines for each synthon a set of all self-consistent sequences of half-reactions, their particular starting materials and their consequent product functionality.
- 5. Eliminate, for each synthon, undesirable sequences:

^{178.} Hendrickson, J.B. J. Am. Chem. Soc. 1975, 97, 5784.

- (a) Sequences unsuitable for the synthon skeleton (at sites other than construction sites), which must bear functionality, $f = 4 \sigma$.
- (b) Unavailable starting materials.
- (c) Unacceptable product functionality for the target structure.
- (d) Exclusion of certain functionality in rings (e.g., triple bonds) and certain reactions (cf. Grignard) for cyclizations.
- (e) other criteria, such as implicit refunctionalization or regiospecificity in sequences.
- 6. Select a prime synthon, with the most construction sites, and match successive constructions serially with the other synthons as dictated by the bondset, accepting only matching half-reactions of opposite polarity, to create full synthetic routes.
- 7. Eliminate matchings in which subsequent constructions on one synthon are not compatible with existing functionality on any other synthon already linked to it.

Hendrickson provided details for several of these criteria, which are instructive to a chemist beginning the disconnection process.

1a: A particular skeletal bond is identified, defined by the functional group (or pair of groups) examined.¹⁷¹ These may be summarized (Table 10.4)¹⁷¹ as a function of the position of the functionalized sites on the target skeleton. Some bonds will have a higher priority if the target functionality is exactly correct for certain constructions, or if more constructions are available to yield the particular sites of functionality.¹⁷⁸ A more detailed table of construction bond data is available.¹⁸²



 Table 10.4. Construction of Bonds Dictated by Product Functionality

1b: Certain considerations of the skeleton define particular bonds to be considered for construction. (I) The first is the presence of the skeleton in available starting materials of

recognizable large skeletal units such as aromatic rings or monoterpenes for sesquiterpene synthesis. (2) The second is division into two or three similar sized skeletons for convergent synthesis efficiency (*divide* each *target into two disconnect fragments at each retrosynthetic step*). Two or three synthons of similar size may be separately constructed in parallel, then linked. Bonds at or near the center of the skeleton can be used to disconnect the skeleton into separate component synthons. (3) Choose bond pairs for annelation. (4) Inspect for the presence of several like groups that could be introduced simultaneously. (5) Inspect for the presence of skeletal features with limited synthetic choices: quaternary or tertiary centers and small (three- and four-membered) rings. (6) Consider strategic ring disconnections in polycyclic skeletons. (7) Consider stereochemical features.

Hendrickson restated this principle¹⁷¹ in a manner that can be used for planning the first disconnection.

"Fully convergent bondsets of any target skeleton are readily created by dissection of the target into two pieces, then cutting each of these in two again. When all the pieces so obtained also corresponds to skeletons of available starting materials, this creates an ordered bondset for a potential synthesis using those starting materials."

- 2. In the bondsets γ , which is the number of construction reactions in the synthetic sequence, should be minimized to make the synthesis more economical (shorter).
- 3. The pattern of construction sites on any synthon can be defined as to their relative placement or location and the order in which they undergo construction half-reactions.¹⁷¹ The synthon skeletons are marked as construction sites on which is placed the appropriate functionality for actually constructing half-reactions in a self-consistent sequence. The numerical codification for individual half-reactions¹⁸² defines a reactive strand of up to three functionalized carbons out from the construction site. Except for a terminal (primary) construction site ($\sigma = 1$), there is a question as to which strand of carbons from the site bears the activating functionality. Secondary construction sites ($\sigma = 2$) have two choices and tertiary ($\sigma = 3$) have three. A synthesis with three steps having secondary sites to undergo construction ($\alpha\beta\gamma$) has $2^3 = 8$ ways to attach the reactive strand of functionality on the skeleton required for construction.¹⁷¹ Hendrickson¹⁷⁹ provided a table of sequence lists for use in this procedure.
- The process is illustrated in Figure 10.22¹⁶⁶ for testrone (195). The skeletal fragmentations lead to bicyclo[4.4.0]decane (F), the two-carbon fragment (E), and the cyclopentane fragment (D). The appropriate functionalization is also shown in which vinyl chloride (J) is the synthetic equivalent of (E), ketone (K) is the equivalent of F, and 2-methyl-1,3-cyclopentanedione (H) substitutes for (D).

^{179.} Reference 171, pp 101-169.

5-7: These are self-explanatory.



Figure 10.22. A SYNGEN-Generated Retrosynthesis for Testrone. [Reprinted with permission from Hendrickson, J.B. *Accounts Chem. Res.* **1986**, *19*, 274. Copyright © 1986 American Chemical Society.]

Hendrickson's approach can be applied without a computer. However, a beginner does not have the extensive background of reactions or a mental pool of reasonable starting materials and so, without a computer, may not be able to take full advantage of this methodology. The main lesson from this section will point a beginner toward a search for convergent disconnections and the use of an approach that breaks the molecule into two fragments at each disconnection level. Some rationale must be provided as to which two fragments are the best.

10.10.B. Barone's MARSEIL/SOS System

Barone developed an approach that relies on a microcomputer and the program MARSEIL/ SOS (Simulated Organic Synthesis).¹⁸⁰ It aims to be a usable electronic lab notebook for organic synthesis. The fundamental basis of this program is¹⁸⁴ "about 350 reactions which

^{180.} Azario, P.; Barone, R.; Chanon, M. J. Org. Chem. 1988, 53, 720.

constitute about 33% of March and Smith,"¹⁸¹ and it follows a retrosynthetic approach.¹⁸² The structural features of the target are determined in two parts. (1) Rings and standard features such as nucleophilic centers, electron-withdrawing groups, and so on are determined using classical organic chemistry; (2) A file of substructures is available that are matched with the target. In a general sense, both parts are excellent advice to the chemist beginning a disconnection. Attempting to correlate known substructures and reactive fragments can point to which fragmentation makes the most chemical sense.



Figure 10.23. MARSEIL-SOS Generated Retrosynthetic Scheme for Turmerone. [Reprinted with permission from Bertrand, M.P.; Monti, H.; Barone, R. and the Journal of Chemical Education, Vol. 63, **1986**, 624. Copyright 1986, Divison of Chemical Education, Inc.

The actual search for a particular transform requires that one look for a characteristic substructure, evaluating that substructure and providing reactions to build it. The lack of attention to stereochemistry in the target or disconnect products is a major drawback to the program. In one example (Figure 10.23),¹⁸³ this program generated several synthesis pathways for (\pm)-arturmerone (**242**).¹⁸⁴ It was pointed out that the students who used this program must choose the more reasonable path, "after discussion with the instructor."¹⁸⁷ The instructor chose path 6 (Figure 10.24), and it is clear that this program relies on the chemical intuition and knowledge of reactions of an experienced chemist. In this case, the novice will not be able to reasonably choose the best approach. Barone used a retrosynthetic approach to define the logic of Marseil/SOS, and this was contained in another program, **REKEST** (**RE**search for the **KEy ST**ep).¹⁸⁵

Smith, M.B.; March, J. March's Advanced Organic Chemistry, 6th ed.; Wiley-Interscience, Hoboken, New Jersey, 2007.

^{182.} Barone, R.; Chanon, M. Nouv. J. Chim. 1978, 2, 659.

^{183.} Bertrand, M.P.; Monti, H.; Barone, R. J. Chem. Educ. 1986, 63, 624.

⁽a) Grieco, P.A.; Finkelhor, R.S. J. Org. Chem. 1973, 38, 2909; (b) Ho, T.L. Synthetic Commun. 1974, 4, 189;
(c) Park, O.S. Grillasca, Y.; Garcia, G.A.; Maldonado, L.A. Ibid. 1977, 7, 345 and references cited therein.

^{185.} Barone, R.; Chanon, M. Chimia 1986, 40, 436.

The fundamental logic for disconnection is based on a library of stylized reactions, shown in Figure 10.24.¹⁸⁹ Each reaction is a pattern that allows deletion or addition of one or several bonds in the target. The labels A, B, C, and D are any atoms and the disconnections generally involve deletion of one or two bonds. An analysis for **243** is shown in Figure 10.24.¹⁸⁹ Once the choice of reaction has been made, appropriate atoms for A, B, C, and D are determined within the boundaries of atoms that are compatible with real chemical reactions. Clearly, this general approach is of value because the chemist can examine a target for disconnections that follow the reactions in Figure 10.24, which leads to better decisions as to which disconnections should be made. The bonds chosen for disconnection maximize simplification of the target. Bonds are chosen that can easily be chemically formed. A pool of known starting materials and chemical reactions is essential. Once the disconnection process begins, the chemical experience and interest of the chemist will usually determine which pathway is best suited for their purpose.



Figure 10.24. Reaction Types for REKEST and MARSEIL/SOS.

10.11. DEGRADATION TECHNIQUES AS A TOOL FOR RETROSYNTHESIS

10.11.A. Chemical Degradation

Structural information about complex molecules is often obtained by degrading a target into simple, and identifiable pieces. Common methods for degrading a molecule include hydrolysis, thermolysis, photolysis or treatment with chemical reagents. The bonds that break in a breaks are correlated with known reactions by which these bonds can be formed by chemical means. Analysis of degradation products can then be used to construct a complete or partial synthetic tree, or it can point to a key reaction for a potential synthesis.

Bleomycin A_2 (244) was isolated by Umezawa and co-workers,¹⁸⁶ and shown to be a potent anticancer agent. The total synthesis of bleomycin reported by Hecht and co-workers is a

^{186. (}a) Ikekawa, T.; Iwami, F.; Hiranaka, H.; Umezawa, H. J. Antibiot. (Tokyo) 1964, 17A, 194; (b) Umezawa, H.; Maeda, K.; Takeuchi, T.; Okami, Y. Ibid. 1966, 19A, 200; (c) Umezawa, H. Suhara, Y.; Takita, T.; Maeda, K. Ibid. 1966, 19A, 210.

superb example of the chemical degradation approach. While determining the structure, it was shown that hydrolysis and other chemical manipulations of **242** gave nine key fragments: aminopropyldimethyl sulfonium (**245**); 2-aminoethyl-2',4-bithiazole-4'-carboxylic acid (**246**); L-threonine (**247**); (2*R*,3*S*,4*R*)-4-amino-3-hydroxy-2-methylpentanoic acid (**248**); L-*erythro*- β -hydroxy-histidine (**249**); β -amino- β -(4-amino-6-carboxy-5-methylpyrimidin-2-yl)propionic acid (**250**); a rearrangement product, L- β -aminoalanine (**251**); gulose (**252**); and, carbamoyl mannose (**253**).

Hecht's synthetic approach was to first synthesize each of the individual pieces. The total synthesis required connection of the nine molecules to give bleomycin.¹⁸⁷ The disconnected pieces are shown in Scheme 10.21¹⁸⁷ and the plan to synthesize bleomycin from these pieces constitutes an outline of the synthetic tree. Hecht and c-worker's synthesis of bleomycin A_2 is also an excellent example of a convergent synthesis (sec. 10.3.C). Note that Boger synthesized bleomycin using a different strategy.¹⁸⁸



Scheme 10.21. Retrosynthetic Analysis of Hecht's Bleomycin A2 Synthesis.

^{187. (}a) McGowan, D.A.; Jordis, U.; Minster, D.K.; Hecht, S.M. J. Am. Chem. Soc. 1977, 99, 8078; (b) Arai, H.; Hagman, W.K.; Suguna, H.; Hecht, S.M. Ibid. 1980, 102, 6631; (c) Levin, M.D.; Subrahamanian, K.; Katz, H.; Smith, M.B.; Burlett, D.J.; Hecht, S.M. Ibid. 1980, 102, 1452; (d) Hecht, S.M.; Rupprecht, K.M.; Jacobs, P.M. Ibid. 1979, 101, 3982; (e) Ohgi, T.; Hecht, S.M. J. Org. Chem. 1981, 46, 1232; (f) Pozsgay, V.; Ohgi, T.; Hecht, S.M. Ibid. 1981, 46, 3761; (g) Aoyagi, Y.; Suguna, H.; Murugesan, N.; Ehrenfeld, G.M.; Chang, L-H.; Ohgi, T.; Shekhani, M.S.; Kirkup, M.P.; Hecht, S.M. J. Am. Chem. Soc. 1982, 104, 5237; (h) Aoyagi, Y.; Katano, K.; Suguna, H.; Primeau, J.; Chang, L.-H.; Hecht, S.M. Ibid. 1982, 104, 5537.

^{188.} See Boger, D.L.; Cai, H. Angew. Chem. Int. Ed. 1999, 38, 448 and references cited therein.

Reactions other than hydrolysis can fragment a molecule, and the degradation of securinine $(254)^{189}$ in Scheme 10.22 uses other chemical reactions to generate a synthetic tree . Reductive cleavage of the C-N bond yielded 255. The alkene unit was reduced by catalytic hydrogenation to 258, but the lactone unit could also be reduced with LiAlH₄ to give 256. Allylic alcohol 256 was oxidatively degraded to 257 with permanganate. Reduction of 258 liberated 259. Hydrogenation in the presence of base, however, gave 260. Reduction of the lactam carbonyl in 260 with LiAlH₄ gave 261. With this degradation scheme in mind, a retrosynthesis is shown in Scheme 10.23,¹⁹⁰ based on Horii's total synthesis. Note the similarity of 262 (in Scheme 10.23) to 255 and 258, and also the relationship of 263 to 256. Disconnection product 264 yielded the two starting materials, the monoethyleneketal of 1,2-cyclohexanedione (265) and 2-lithiopyridine.



Scheme 10.22. Chemical Degradation of Securinine (254).



Scheme 10.23. Retrosynthetic Analysis of Horii's Securinine Synthesis.

^{189. (}a) Nakano, T.; Yang, T.H.; Terao, S. J. Org. Chem. 1963, 28, 2619; (b) Satoda, I.; Murayama, M.; Tsuji, J.; Yoshii, E. Tetrahedron Lett. 1962, 1199; (c) Saito, S.; Kotera, K.; Shigematsu, N.; Ide, A.; Sugimoto, N.; Horii, Z.; Hanaoka, M. Yamawaki, Y.; Tamura, Y. Tetrahedron 1963, 19, 2085; (d) Nakano, T.; Yang, T.H.; Terao, S. Tetrahedron Lett. 1963, 665 (e) Saito, S.; Kodera, K.; Sugimoto, N.; Horii, Z.; Tamura, Y. Chem. Ind., (London), 1962, 1652.

^{190.} Horii, Z.; Hanaoka, M.; Yamawaki, Y.; Tamura, Y.; Saito, S. Shigematsu, N.; Kotera, K.; Yoshikawa, H.; Sata, Y.; Nakai, H. Sugimoto, N. *Tetrahedron* 1967, 23, 1165.

10.11.B. Retro-Mass Spectral Degradation

A target may resist hydrolysis or chemical degradation, or the degradation products may not yield useful information. An alternative degradation technique is available that uses the ionizing electron beam of a mass spectrometer. The ionization pathways available from electron impact in the mass spectrum are bond fission processes that occur by known and predictable pathways. Indeed, each fragmentation pathway usually follows an analogous chemical reaction pathway *in a retrosynthetic manner*. It therefore follows that an examination of mass spectral ionization patterns can give clues for suitable disconnections and a synthetic tree.

This basic premise was outlined by Kametani and Fukumoto,¹⁹¹ and used for the synthesis of several alkaloids. As mentioned, the key feature of the analysis is the fact that many chemical reactions appear as their retro analog in the mass spectrum. These retro reactions are disconnections that can be translated directly to a synthetic tree. Some examples of retroreactions that have been identified in the mass spectrum are (1) retro-Diels-Alder (sec. 11.5.B),¹⁹² (2) a retro-1,3-dipolar addition (sec. 11.11),¹⁹³ (3) a retro Wagner-Meerwein (sec. 12.2.B),^{194,195} and (4) a retro-Ritter reaction.¹⁹⁶ The **Ritter reaction**¹⁹⁷ couples an alkene and a nitrile to give an amide.

Kametani has applied retro-mass spectral analysis to total synthesis. The mass spectra of tetrahydroisoquinoline alkaloids show fragmentations by the three major pathways shown in Scheme 10.24.¹⁹⁵ Kametani observed that path c (a retro Diels-Alder reaction) was the major fragmentation pathway (sec. 11.5.B).¹⁹⁵ Xylopinene (**266**) gave this specific fragmentation (to **267** and **268**),¹⁹⁸ and Scheme 10.25¹⁹⁵ shows the resulting total syntheses reported by Kametani, based on the Diels-Alder reaction suggested by path c in Scheme 10.24 and the observed fragmentation pattern. Two related synthetic routes involve thermal conversion of benzocyclobutane derivatives to a diene (sec. 11.10.F) that reacts with the dihydroisoquinoline starting material (**269**). In one case, heating cyano derivative **270** gave a transient diene (**271**) that reacted with **269** to give the Diels-Alder adduct **272**.¹⁹⁹ In the second case, alcohol **273** was heated to generate **274**, which reacted with **269** to give **275**.²⁰⁰ Reduction of either **272** or **275**

192. Bel, P.; Mandelbaum, A. Org. Mass. Spectrom. 1981, 16, 513.

194. Wolfshütz, R.; Schwarz, H.; Blum, W.; Richter, W.J. Org. Mass. Spectrom. 1979, 14, 462.

196. Nagubandi, S. Org. Mass. Spectrom. 1980, 15, 535.

- 199. (a) Kametani, T.; Takahashi, T.; Honda, T.; Ogasawara, K.; Fukumoto, K. J. Org. Chem. 1974, 39, 447; (b) Kametani, T.; Kajiwara, M. Takahashi, T.; Fukumoto, K. J. Chem. Soc. Perkin Trans. 1 1975, 737.
- 200. Kametani, T.; Katoh, Y.; Fukumoto, K. J. Chem. Soc. Perkin Trans. 1 1974, 1712.

^{191.} Kametani, T.; Fukumoto, K. Acc. Chem. Res. 1976, 9, 319.

^{193.} Selva, A.; Traldi, P.; Fantucci, P. Org. Mass Spectrom. 1978, 13, 695.

^{195.} Smith, M.B.; March, J. *March's Advanced Organic Chemistry, 6th ed.*, Wiley-Interscience, Hoboken, New Jersey, *2007*, pp 1580-1585 and references cited therein.

^{197. (}a) Krimen, L.I.; Cota, D.J. Org. React. 1969, 17, 213; (b) Ritter, J.J.; Minieri, P.P. J. Am. Chem. Soc. 1948, 70, 4045; (c) Ritter, J.J.; Kalish, J. Ibid. 1948, 70, 4048.

^{198.} Budzikiewicz, H.; Djerassi, C.; Williams, D.H. Structure Elucidation of Natural Products by Mass Spectrometry, Vol. 1, Holden-Day, San Francisco, 1964.

gave **266** in good yield. The carbocyclic analog of this reaction^{201,202} had been used previously in synthesis, and Oppolzer had previously used the amido analog of this condensation reaction for alkaloid synthesis (sec. 11.10.F).²⁰³ Its use by Kametani in this case, however, was the direct result of construction of a synthesis tree from the mass spectrum.



Scheme 10.24. Kametani's Mass Spectral Analysis of Tetrahydroisoquinoline Alkaloids. [Reprinted with permission from Kametani, T.; Fukumoto, K. *Accts. Chem. Res.* **1976**, *9*, 319. Copyright © 1976 American Chemical Society.]



Scheme 10.25. Synthesis of Xylopinene (266) Based on Retro-Mass Spectral Analysis.



201. Klundt, I.L. Chem. Rev. 1970, 70, 471.

202. Kametani, T.; Takahashi, T.; Ogasawara, K.; Fukumoto, K. Tetrahedron 1974, 30, 1047.

203. (a) Oppolzer, W. J. Am. Chem. Soc. 1971, 93, 3834, 3833; (b) Oppolzer, W.; Keller, K. Ibid. 1971, 93, 3836; (c) Oppolzer, W. Tetrahedron Lett. 1974, 1001.

The availability of mass spectrometers, and variety of mass spectrometric techniques and detectors clearly makes this an attractive tool for retrosynthetic analysis. The major drawback is that structural identification of the mass spectral fragment is a necessity, which is often unknown and its determination can require fragmentation studies on isotopically labeled compounds. Modern mass spectrometry allows the use of *mass spectrometry of mass spectrometry* to identify fragments, and with the high-resolution mass spectrometers capable of identifying the mass of individual fragments, identification of key fragments is often possible. This analytical technique brings retro-mass spectral analysis into the fold of modern methods for determining a retrosynthesis tree. If the structure of a fragment is not easily determined, however, this approach will be of little value for constructing a synthetic tree. If the fragment is known, retro-mass spectral analysis can be a useful tool.

10.12. COMBINATORIAL CHEMISTRY

Combinatorial chemistry is a term used to describe various microscale methods of solidstate synthesis and testing. It involves the synthesis of large numbers of compounds (called libraries), by doing reactions in a manner that produces large combinations of products, usually as mixtures.²⁰⁴ This approach has been called *irrational drug design*, since early approaches involved making a large vat of all possible chemical combinations of several reactants. Compare this with parallel synthesis, where the same reactions are repeated separately to produce many individual but related products. In other words, a parallel synthesis means that a compound library is constructed by synthesizing many compounds in parallel, keeping each compound in a separate reaction vessel. When the final compounds are kept separate in this manner, their identity is easily discerned. The pin-method of combinatorial synthesis, described below, is one such parallel synthesis method. Libraries of compounds can also be generated by pooling strategies, and the teabag method described below illustrates this type of approach. The methods of combinatorial synthesis will be described below, but there are several strategies for efficient synthesis of a target illustrated by the cartoons in Figure 10.25.^{208c} The first strategy (A) is one where doubly functionalized monomer units are linked in peptide synthesis and other oligomer synthesis. In strategy B, the synthesis begins with a template that is already equipped with several functional groups. Different building blocks are attached through these groups in a series of separate steps or in one pot. In strategy C, the reactions introduce new functionality in the product. As each new functional group is added, that product becomes the template for the next reaction. Combinatorial syntheses can be performed both in solution and on a solid support.

^{204. (}a) Czarnik, A.W.; DeWitt, S.H. (Eds.), A Practical Guide to Combinatorial Chemistry, Amer. Chem. Soc. Washington, D.C., 1997; (b) Chaiken, I.N.; Janda, K.D. (Eds.), Molecular Diversity and Combinatorial Chemistry: Libraries and Drug Discovery, American Chemical Society, Washington, D.C., 1996; (c) Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. Angew. Chem. Int. Ed. 1996, 35, 2289; (d) Thompson, L.A.; Ellman, J.A. Chem. Rev. 1996, 96, 555; (e) Pavia, M.R.; Sawyer, T.K.; Moos, W.H. (Eds.), Bioorg. Med. Chem. Lett. Symposia-in-print no. 4, 1993, 3, 381.



Figure 10.25. Strategies in Combinatorial Synthesis. [Reprinted with permission from Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed.* **1996**, *35*, 2289.]

In 1963 Merrifield introduced solid-state synthesis for the synthesis of peptides.²⁰⁵ This technique involves chemical functionalization of a polystyrene bead (or another polymeric bead) that reacts with the carboxylic acid portion of a *N*-protected amino acid to give a polymerbound amino ester such as **276**. When **276** is treated with a reagent to deprotect the amine, it can react with another N-protected amino acid, activated at the carbonyl, to give a dipeptide. This procedure can be repeated to generate the desired polypeptide, and when the target has been attained a reagent is added to cleave the polypeptide from the bead (hydrolysis). This solid-state synthesis can be applied to other types of chemical transformations.²⁰⁶

$$\begin{array}{c} & & \\ & &$$

The fundamental idea of the Merrifield solid-state synthesis can be extended, using several beads where each is attached to a different amino acid (V, I, S, etc.)²⁰⁷ Subsequent reaction can generate a "pool" of peptides. If this mixture of beads was treated with three activated amino acids (V, I, S), a total of nine products would be generated, each one attached to a bead, as shown in Figure 10.26. This approach can be expanded to generate a large number of peptides. If the bead containing V were made to react with 20 different amino acids, a mixture of 20 dipeptides would be generated. If each of these 20 dipeptides were to react with 20

^{205.} Merrifield, R.B. J. Am. Chem. Soc. 1963, 85, 2149.

^{206. (}a) Crowley, J.I.; Rapoport, H. Acc. Chem. Res. 1976, 9, 135; (b) Leznoff, C.C. Acc. Chem. Res. 1978, 11, 327.

^{207.} The 3-letter codes and the appropriate 1-letter code for the essential amino acids are given here. glycine (gly, G), alanine (ala, A), valine (val, V), leucine (leu, L), isoleucine (ile, I), phenylalanine (phe, F), serine (ser, S), threonine (thr, T), tyrosine (tyr, Y), cysteine (cys, C), methionine (met, M), asparagine (asn, N), glutamine (gln, Q) aspartic acid (asp, D), glutamic acid (glu, E), lysine (lys, K), tryptophan (trp, W) histidine (his, H), arginine (arg, R), proline (pro, P).

different amino acids, 20 x 20 or 400 tripeptides would be generated as a mixture. If this 400 member tripeptide library were to react with 20 amino acids, a mixture of 20 x 20 x 20, or 8000 tetrapeptides, would be generated. If we continued this process, 20^4 (160,000) pentapeptides, 20^5 (3,200,00) hexapeptides, 20^6 (1,280,000,000) heptapeptides, and 20^7 (25,600,000,000) octapeptides would be generated; a huge library of compounds all mixed together.²⁰⁸ It is easy to imagine variations that would build other libraries. A mixture of the three amino acids shown in Figure 10.26, for example, could be mixed with 20 amino acids and this would generate 60 dipeptides. This library of dipeptides could be reacted with 20 amino acids to generate 60^{20} different tetrapeptides (3.656 x 10^{35}) compounds, which would be a library from a library.



Figure 10.26. Generation of a Nine-Component Dipeptide Library.

Early in the development of combinatorial chemistry it was discovered that when chemical reactions occurred close to the polymer bead there were problems, both in chemical reactivity and in releasing the final product from

the bead. An important variation added
a *spacer* between the bead and the
functional group used for chemistry.
$$277$$

Hydrocarbon chains connected to the ether linkage (as in 277) diamide groups, and polyamide chains such as 278 are commonly used. The group is usually be attached to the bead by an acid-labile unit, or one that is susceptible to enzymatic cleavage. Two common, and highly acid-labile anchors are the aryl derivatives 4-(2',4'-dimethoxyphenylhydroxylmethyl)phenoxy (279) or 2-methoxy-4-alkoxybenzyl (280).²⁰⁹



^{208. (}a) Nielsen, J. Chem. Ind. 1994, 902; (b) Sepetov, N.F.; Krchák, V.; Stanková, M.; Wade, S.; Lam, K.S.; Lebl, M. Proc. Natl. Acad. Sci. USA 1995, 92, 5426.

^{209. (}a) Rink, H. Tetrahedron Lett. 1990, 28, 3787; (b) Barlos, K.; Gratos, D.; Kallitsis, J.; Papaphotiu, G.; Sotiriu, P.; Wenqing, Y.; Schäfer, W. Tetrahedron Lett. 1989, 30, 3943.
A reasonable question is how is the combinatorial technique done experimentally? Two methods will be presented here to illustrate the fundamental techniques. Houghten described a teabag method²¹⁰ that could prepare as many as 150 different peptides with a yield of up to 50 mg.²¹¹ A polypropylene bag (see Figure 10.27)²¹⁵ is charged with \approx 100 mg of a polymeric support (usually polystyrene-1% divinylbenzene). Each bag contains a label and is immersed in a polyethylene bottle containing piperidine/DMF. A computer-automated device adds amino acids, and the peptide is generated within each teabag. Treatment of the bags with a deprotection reagent and subsequent washing liberates the peptides.



Figure 10.27. The Teabag Approach to Combinatorial Peptide Synthesis. [Reprinted with permission from Jung, G.; Beck-Sickinger, A.G. *Angew. Chem., Int. Ed.* **1992**, *31*, 367.]

A second technique that accomplishes peptide synthesis on polyethylene rods was developed by Geyson et al.²¹² A typical array of rods (called pins) consists of 96 pins (typically 4 mm in diameter and 40 mm in length),²¹⁵ arranged in 8 rows of 12 rods (see Figure 10.28b). The pins fit into the wells of plates (see Figure 10.28),²¹⁵ which were developed for the enzyme-linked immunosorbent assay (ELISA). The polyethylene rods are functionalized with acrylic acid, and N^{β}-Fmoc- β -alanyl-1,6-diaminohexane is attached as a spacer (see Figure 10.28a). The idea is to attached an amino acid to each of the pins, and place the solution containing the reactants into the wells. The pins are dipped into the wells and allowed to react. To deprotect the terminal

^{210.} Houghten, R.A. Proc. Natl. Acad. Sci. USA 1985, 82, 5131.

^{211.} Jung, G.; Beck-Sickinger, A.G. Angew. Chem. Int. Ed. 1992, 31, 367.

^{212.} Geysen, H.M.; Meloen, R.H.; Barteling, S.J. Proc. Natl. Acad. Sci. USA 1984, 81, 3998. Also see Kerr, J.M.; Banville, S.C.; Zukermann, R.N. Bioorg. Med. Chem. Lett. 1993, 3, 463

position, deprotection reagent is added to a new plate of wells, and the pins are dipped into that. Since the "polyethylene rods cannot swell or shrink, and adsorbed molecules can only be removed with difficulty, thorough washing after each reaction step of the synthesis cycle is of utmost importance".²¹⁵ Recent work has shown that soft, but mechanically strong polymer rods derived from styrene-divinylbenzene copolymers prepared by adjusting the reaction conditions,²¹³ could be cut into disks with good swelling characteristic in various solvents, and that resist osmotic shock. Such disks are an alternative support for solid phases synthesis.



Figure 10.28. The Pin Approach to Combinatorial Peptide Synthesis. [Reprinted with permission from Jung, G.; Beck-Sickinger, A.G. *Angew. Chem., Int. Ed.* **1992**, *31*, 367.]

Chemical reactivity is an important consideration. If a bead reacts with many different reactants (*n* coupling partners), there will be *n* products, which is also a problem in solution combinatorial synthesis. Individual substances can be obtained by fast parallel syntheses, that is, *n* substances are synthesized in *n* reaction vessels.^{208c} Since it is reasonable that some reactants will react faster, and in higher yields than others, there may be different *amounts* of the *n* products. In other words, some coupling reactions occur at faster rates than others. This problem of different reaction rates can be avoided by the so-called *split method*.^{214,228} As shown in Figure 10.29,^{208d} the solid support is divided into three equal parts in this case, and each of these is treated with a component A. The resulting products are mixed and divided again, giving three mixtures in which the resin-linked components (A¹, A¹, A³) are present in equimolar amounts. When these are treated with new reagents (B¹, B², B³), nine defined products are produced. Since there is only one reactant in solution in each reaction vessel at any one time, all reactions proceed to completion, despite possible differences in kinetics.^{208c} Repetition of the cycle of division, reaction, and mixing gives large compound libraries in

^{213.} Hird, N.; Hughes, I.; Hunter, D.; Morrison, M.G.J.T.; Sherrington, D.C.; Stevenson, L. Tetrahedron 1999, 55, 9575.

^{214.} Sebestyén, F.; Dibó, G.; Kovács, A.; Furkua, A. Bioorg. Med. Chem. Lett. 1993, 3, 413.

which all compounds are present in equimolar amounts. Ley and co-workers developed an approach for the rapid automated optimization of polymer-supported reagents in synthesis using an optimized set of reaction conditions with an array of 80 compounds.²¹⁵



Figure 10.29. Split Synthesis Method. [Reprinted with permission from Thompson, L.A.; Ellman, J.A. *Chem. Rev.* **1996**, 96, 555. Copyright © 1996 American Chemical Society.]

An important component of the split method is *deconvolution*. The library formed by these methods will be a mixture, and when the mixture must be tested in solution structure determination can be very difficult. An example of deconvolution is shown in Figure 10.30^{208c} for a molecule with four variable substituents (A-D), where five different possibilities for each substituent lead to a total library of $5^4 = 625$ compounds. In the first deconvolution, 25 sublibraries are synthesized, each containing 25 compounds, where the substituents A and B are defined. Using a predetermined measure of activity (which compounds are being targeted), the most active sublibrary contains the optimal combination of substituents A and B, A^2B^1 in Figure 10.30. Based on this, five further sublibraries in the form $A^2B^1C^nC^{1.5}$ are prepared,^{208c} each containing five components in which C is now defined. The optimal residue D is determined in the last step by synthesis of the five individual compounds in the form A²B¹C³Dⁿ, and in Figure 10.30, the most active compound was A²B¹C³D⁵.^{208c} To get around the need for a new synthesis of another sublibrary for each assay of the total library. Han, et al. used a procedure called recursive deconvolution.²¹⁶ An aliquot is held back after each cycle of the split synthesis. From active mixtures, similarly in one or more steps, the single active compound is identified.^{208c} No new split syntheses are involved since only the intermediates retained during the first split synthesis need to be elaborated further.^{208c}

^{215.} Jamieson, C.; Congreve, M.S.; Emiabata-Smith, D.F.; Ley, S.V. Synlett 2000, 1603.

^{216. (}a) Han, H.; Wolfe, M.; Brenner, S.; Janda, K.D. Proc. Natl. Acad. Sci. USA 1995, 92, 6419; (b) Erb, E.; Janda, K.D.; Brenner, S. Proc. Natl. Acad. Sci. USA 1994, 91, 11422.



Figure 10.30. Identification of the Most Active Library Component by Deconvolution. [Reprinted with permission from Balkenhol, F.; von dem Bussche-Hünnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem. Int. Ed.* **1996**, *35*, 2289.]

It is reasonable to ask is how each product of a massive library can be identified as a unique entity, and isolated? There are several techniques by which this can be accomplished. All products can be detached from the beads and isolated as a mixture. This mixture can be analyzed using high performance liquid chromatography (HPLC) and gas chromatography (GC) techniques, particularly when combined with mass spectrometry (HPLC/mass spectrometry and GC/mass spectrometry). In principle, each component can be separated and identified.^{214,217} Direct monitoring of solid-phase reactions, on the bead itself without prior cleavage from the resin, is possible using soft laser desorption time-of-flight mass spectrometry, if photocleavable phenacyl ester or *o*-nitroveratryl linker groups are used.²¹⁸ Lam and co-workers reported a "one-bead-

^{217.} For examples of peptide analysis using these techniques, see (a) Hean, M.T.W.; Regnies, F.E.; Wehr, C.T (Eds.), *High Performance Liquid Chromatography of Proteins and Peptides*, Academic Press, New York, **1983**; (b) Hean, M.T.W. *Adv. Chromatogr.* **1982**, *20*, 1; (c) Bruins, A.P.; Covey, T.R.; Henion, J.D. *Anal. Chem.* **1987**, *59*, 2642; (d) Bruins, A.P.; Weidolf, O.G.; Henion, J.D.; Buddle, W.L. *Anal. Chem.* **1989**, *59*, 2647; (e) Grolo, M.; Takeuchi, T.; Ishii, D. *Adv. Chromatogr.* **1989**, *30*, 167.

^{218.} Gerdes, J.M.; Waldmann, H. J. Comb. Chem. 2003, 5, 814.

one-compound" encoding approach, based on mass spectrometry.²¹⁹ As stated by Lam, prior to library synthesis the inner core of each bead is derivatized with 3-4 different coding blocks on a cleavable linker.²²³ An individual coding block that contains a functional group with the same chemical reactivity encodes each functional group on the scaffold.²²³ During the library synthesis, the same chemical reactions take place on the scaffold (outer layer of the bead) and coding blocks (inner core of the bead) concurrently.²²³ After screening, the coding tags in the positive beads are released, followed by mass determination of the moelcuels using matrix-assisted laser desorption ionization (MALDI) Fourier transform mass spectrometry.²²³



It would be useful to know the bead to which each product is attached. A solution to this problem is the use of a molecular tag, work pioneered by Brenner and Lerner in 1992,²²⁰ and by Nielsen.^{221,212} The idea is to give a binary chemical tag for each reagent. In the work of Still and co-workers, a constant segment of a library is attached to a polymeric bead using standard solid-phase methods.²²² A tag for the first reagent is attached, and then the amino acid is attached. After processing, a second tag is attached, followed by the second amino acid in the sequence. Still and co-worker's coding strategy used haloaromatic tags such as 281.^{226,208d} When attached as an amide, the chain length (n) can be varied along with the haloaryl ether unit, to create a binary synthesis code. The reagents can be designated in binary as 001 (reagent 1), 010 (reagent 2), 011 (reagent 3), to 111 (reagent 7). If reagent 3 were used in the first step and reagent 1 in the second and reagent 6 in the third, the description would be 001 011 011.²²⁶ In 281, nine different haloaryl units could be attached to create nine tags, T¹-T⁹ and each could be linked to one reagent. Therefore, aryl halide A might be 001 (T¹), B 002 (T²), and C 011 (T⁶) and so on. Two possibilities are pentachlorophenyl and 2,4,6-trichlorophenyl. Using different haloaromatic units results in a large number of unique tags. As the peptide chain grows, each tag gives the exact sequence of that chain. In this case, any attached tag can be detached by UV and decoded by electron capture GC. Still and co-workers related the tagging molecules to the binary bits of the synthesis code by arranging them $(T^{1}-T^{9})$ in order of their GC elution order where

^{219.} Song, A.; Zhang, J.; Lebrilla, C.B.; Lam, K.S. J. Am. Chem. Soc. 2003, 125, 6180.

^{220.} Brenner, S.; Lerner, R.A. Proc. Natl. Acad. Sci. USA 1992, 89, 5381.

^{221.} Nielsen, J.; Brenner, S.; Janda, K.D. J. Am. Chem. Soc. 1993, 115, 9812.

Ohlmeyer, M.H.J.; Swanson, R.N.; Dillard, L.W.; Reader, J.C.; Asouline, G.; Kobayahsi, R.; Wigler, M.; Still, W.C. Proc. Natl. Acad. Sci. USA 1993, 90, 10922.

 T^1 is retained the longest on the GC column used and designates the rightmost bit of the binary synthesis code.²²⁶ In this way, the tags are easily identified and the product can be identified.

An interesting solution is to color code the beads and the vessel in which the reaction is done.²²³ If there were eight subunits, for example, each one could be partitioned into different containers with different color caps. If each subunit were attached to a different color bead, one bead of each color could be added to each color-coded vessel. When the next subunit is attached, the compounds formed can be sorted individually by cap and by color. This process can be contained as each new subunit is attached. Another color-coded approach can be used to identify products that are susceptible to a particular chemical reaction. The approach couples the acceptor molecule to an enzyme such as alkaline phosphatase or to a fluorescent, and then adds these in soluble form to generate the peptide-bead library.²²⁴ Those beads that contain compounds active for this analysis will be stained and are usually visible to the naked eye or under a low-power microscope. The stained beads can then be removed for analysis. In one reported study, a monoclonal antibody active against β -endorphin was of interest because it had a high affinity for the epitope sequence UCCF,²²⁷ and six reactive beads were obtained from 2 million screened beads from a pentapeptide library.

A powerful method to identify individual components of a combinatorial library is known as encoded combinatorial chemistry. Brenner and Lerner²²⁴ designed a method where each chemical sequence is labeled with a so-called genetic tag (nucleotide sequences), and each tag is constructed by chemical synthesis. A monomeric chemical unit is attached to a polymeric structure and this is followed by addition of an oligonucleotide sequence. The sequence of that oligonucleotide constitutes a tag. Active products from the library are selected by binding to a receptor. After the chemical entity is bound to a target, the genetic tag can be amplified by replication, and utilized for enrichment of the bound molecules by serial hybridization to a subset of the library.²²⁴ The nature of the chemical structure bound to the receptor is decoded by sequencing the nucleotide tag.²²⁴ Another encoding technique is illustrated by synthesizing a peptide and a nucleotide chain in an alternating, bidirectional manner.²¹² Sequencing the nucleotide chain the sequence of the peptide chain.

This chapter concerns synthesis. How is combinatorial chemistry pertinent to this discussion? Many small molecules can be synthesized using combinatorial techniques and evaluated for biological activity. One example is the synthesis of substituted benzodiazepines such as **282**, shown in Scheme 10.26.²²⁵ This approach has become important ro the pharmaceutical industry

^{223.} Guiles, J.W.; Lanter, C.L.; Rivero, R.A. Angew. Chem. Int. Ed. 1998, 37, 926.

^{224.} Lam, K.S.; Salmon, S.E.; Hersh, E.M.; Hruby, V.J.; Kazmierski, W.M.; Knapp, R.J. Nature 1991, 354, 82.

^{225. (}a) Bunin, B.A.; Plunkett, M.J.; Ellman, J.A. Proc. Natl. Acad. Sci. USA 1994, 91, 4708. Also see (b) DeWitt, S.H.; Kiely, J.S.; Stankovic, C.J.; Schroeder, M.C.; Cody, D.M.R.; Pavia, M.R. Proc. Natl. Acad. Sci. USA 1993, 90, 6909.

for drug discovery.226



Scheme 10.26. Combinatorial Synthesis of Benzodiazepines.

Many combinatorial-based syntheses have been reported.²²⁷ Schreiber and co-workers described a synthesis strategy that yielded diverse small molecules by combinatorial techniques.²²⁸ Andrus and co-workers, with the goal of multidrug resistance reversal, have prepared a solution-phase indexed combinatorial library of nonnatural polyenes such as **283**.²²⁹ Varying R and R¹ in **283** generated this library. Ellman and co-workers reported a combinatorial library of synthetic receptors targeting vancomycin-resistant bacteria,²³⁰ and Paterson and co-workers prepared polyketide-type libraries by iterative asymmetric aldol reactions on a solid support.²³¹ Rieser and co-workers used combinatorial liquid-phase synthesis to prepare [1,4]-oxazepine-7-ones by the Baylis-Hillman reaction (see sec. 9.7.B).²³² Schreiber and co-workers reported the synthesis and evaluation of a library of polycyclic small molecules for use in chemical genetic assays.²³³ Bauer and co-workers reported a library of *N*-substituted 2-pyrazoline compounds such as **284**, by parallel solution-phase synthesis, for screening as therapeutic agents as antibacterials, antivirals, and anti-inflammatory compounds.²³⁴ Libraries of trisaccharides have been prepared by combinatorial methods.²³⁵ Han and co-workers reported highly substituted thiophene derivatives such as **285** as novel phosphodiesterase-4 (PDE-4) inhibitors,²³⁶ and Ley

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- 232. Räcker, R.; Döring, K.; Reiser, O. J. Org. Chem. 2000, 65, 6932.
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⁽a) Gallop, M.A; Barrett, R.W.; Dower, W.J.; Fodor, S.P.A.; Fordon, E.M. *J. Med. Chem.* 1994, 37, 1233;
(b) Gordon, E.M.; Barrett, R.W.; Dower, W.J.; Fodor, S.P.; Gallop, M.A. *J. Med. Chem.* 1994, 37, 1385;
(c) Alper, J. *Science*, 1994, 264, 1399;
(d) Houghten, R.A.; Pinilla, C.; Blondelle, S.E.; Appel, J.R.; Dooley, C.T.; Cuervo, J.H. *Nature (London)* 1991, 354, 84.

For reviews, see Dolle, R.E.; Le Bourdonnec, B.; Morales, G.A.; Moriarty K.J.; Salvino, J.M. J. Comb. Chem. 2006, 8, 597; Dolle, R.E. J. Comb. Chem.; Idem 2005, 7, 623; 2004, Idem 6, 623; 2003, 5, 693; Idem 2002, 4, 369; Idem 2001, 3, 477; Idem 2000, 2, 383.

^{236.} Han, Y.; Giroux, A.; Lépine, C.; Laliberté, F.; Huang, Z.; Perrier, H.; Bayly, C.I.; Young, R.N. *Tetrahedron 1999*, *55*, 11669.

and co-workers reported the solution phase synthesis of functionalized bicyclo[2.2.2]octanes.²³⁷ Libraries of heterocyclic compounds have been prepared from peptides and polyamides.²³⁸ Wolf and Hawes also showed that combinatorial techniques are useful for high-throughput screening of enantioselective catalysts, allowing rapid evaluation of their utility.²³⁹



^{237.} Ley, S.V.; Massi, A. J. Chem. Soc. Perkin Trans. 1 2000, 3645.

^{238.} Nefzi, A.; Ostresh, J.M.; Yu, J.; Houghten, R.A. J. Org. Chem. 2004, 69, 3603.

^{239.} Wolf, C.; Hawes, P.A. J. Org. Chem. 2002, 67, 2727.

10.13. CONCLUSION

This chapter summarized general approaches to the total synthesis of complex molecules. These techniques can just as easily be applied to simple molecules, and to short synthetic sequences. One must remember that the concepts of conformational control, regio- and stereochemical control, and steric considerations (discussed in all previous chapters) must be an integral part of the planning at each step of a synthesis. These concepts should be applied to every disconnection. Planning is essential.

The key steps of a synthesis usually involve formation of carbon-carbon bonds. In Chapters 8 and 9, nucleophilic methods involving the disconnect product C^d were discussed in detail. In the chapters that follow, methods of forming carbon-carbon bonds by pericyclic reactions (disconnect products that arise from breaking more than one bond), and by reactions that have cationic intermediates (C^a disconnect products) or radical intermediates (C^{\bullet} disconnect products-carbenes are included in this chapter) will be presented. In each chapter, additional examples of synthetic strategy using those particular reactions will be presented.

HOMEWORK

NOTE: For some problems you may need to consult chapters 11-13 for reactions not yet covered. The focus is on strategy and planning as much as on chemical reactions. Consult your instructor if necessary.

1. For each of the following literature syntheses. (1) Determine the total number of steps and the percentage yield for each of the carbon-carbon bond-forming steps. (2) Identify all powerful reactions-justify each choice in the context of that synthesis. (3) Determine the number and percentage yield for all protection-deprotection steps (if any). (4) Discuss why each protecting group was chosen for that particular application.



2. For each of the following: (1) Determine the strategic bonds. (2) Give two different retrosyntheses based on two different first disconnections. (3) Show all donor and acceptor sites in each disconnect fragment. (4) Give a synthesis for each molecule based on <u>one</u> of your strategic bonds. Choose a starting material that is commercially available with at

most five carbons. (Give the cost per gram of that starting material.).



3. For each of the following: (1) Determine the strategic bonds. (2) Devise a retrosynthetic scheme based on a consecutive strategy. (3) Devise a retrosynthetic scheme based on a convergent strategy. (4) Show a total synthesis based on <u>both</u> (2) and (3).



4. For each of the following, show a reasonable retrosynthetic analysis that gives a starting material with a reasonable cost (current chemical catalog). Show the complete synthesis. Assume an average yield of 75% for each step. What is the overall percentage yield for your synthesis? How many grams of your starting material do you need in order to synthesize 1 gram of the target?



5. Synthesize each of the following from starting materials of at most six carbons (cite chemical catalog and price per gram):



6. Suggest a complete synthesis of the molecule shown (spongidipepsin) from any starting material of no more than six carbons. Show your retrosynthetic analysis, all intermediate products and all reagents.



7. Suggest a complete synthesis of the molecule shown (spirofungin A) from any reasonable starting material. Show your retrosynthetic analysis, all intermediate products and all reagents.



8. For each of the following show a synthesis of the designated starting material to the indicated target. Show all reagents and intermediate products.



9. Construct a retrosynthetic tree based on the given template as a starting material.





- 10. Plumet published a synthesis of (+)-7-deoxypancratistatin, starting with furan as a starting material (see *Org. Lett.* **2000**, *2*, 3683). Draw the retrosynthesis from this paper and compare and contrast it with those syntheses given in Section 10.7. Pay particular attention to strategic bonds and to strategy.
- 11. In a review article (*Synthesis* **1998**, 1559), Chanon presents 8 different syntheses of silphinene and 18 different syntheses of hirsutene. Based on your definitions of efficiency, cost of starting materials, control of stereochemistry, and so on, compare and contrast these syntheses. Draw a conclusion as to which you believe to be the best for each target.
- 12. In 1992, Sir John Cornforth presented a lecture entitled *The Trouble with Synthesis* (see *Aust. J. Chem., 1993, 46, 157*). Read the article and consider the points made in the context of this chapter, particularly those quoted by Corey and Deslongchamps early in the chapter. Also see *Aldrichimica Acta, 1994, 27, 71*.
- 13. Each reference discusses a proposed biosynthetic pathway for the molecule shown. Construct a retrosynthetic tree based on that pathway and then show the total synthesis.





14. Each of the following references give mass spectral fragmentation information for the molecule shown. Construct a retrosynthetic tree based on this information and then give the total synthesis.



15. Each reference describes a chemical degradation of that structure. Construct a retrosynthetic tree based on that degradation scheme and then show the total synthesis.



16. Devise a synthesis for the following molecules showing all chemical steps and reagents. The literature reference given with each molecule refers to its isolation and structure determination, not its synthesis.



17. For each of the following, use a convergent strategy to devise a synthetic scheme. Show the total synthesis based on that scheme.



18. Search the literature to find four <u>different</u> syntheses of the molecule epothilone. Compare and contrast them. Can you devise a new approach?

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chapter Pericyclic Carbon-Carbon Bond Forming Reactions: Multiple Bond Disconnections

11.1. INTRODUCTION

Reactions involving ionic or highly polarized compounds comprise the majority of organic reactions, as seen in other chapters. Chapters 8 and 9 discussed methods for making carbon bonds via nucleophilic carbon species. Chapter 12 will discuss carbon-carbon bond formation with reagents involving electrophilic carbon, and chapter 13 will discuss making carbon-carbon bonds via radical, carbene, and related processes. The reactions in these chapters involve one-carbon disconnections for the most part. There are reactions that involve two-bond disconnections, however, which lead to disconnect products that are readily assembled by known reactions. Many of these reactions generate carbon-carbon bonds by electronic reorganization of molecules, rather than via ionic or radical species in what are generically cal led **pericyclic reactions**. The **Diels-Alder reaction**, **Claisen rearrangement**, and the **Cope rearrangement** fall into this category. Without question, the synthetic utility of these reactions ranks them among the highest in importance. This chapter will focus on methods that use pericyclic reactions, and it will present a brief overview of the mechanistic basis for each reaction. As in previous chapters, however, the emphasis will be on the synthetic utility of each reaction.

11.2. FRONTIER MOLECULAR ORBITAL THEORY

11.2.A. Frontier Orbitals

This chapter deals with molecules containing π bonds: alkenes, dienes, carbonyls, imines, nitriles, and so on. In a typical alkene, bonding is described in terms of the σ - and π -orbitals. Electronic interactions are represented by the molecular orbitals, using σ -orbitals (sp² hybridized



for alkenes, 1) and π -orbitals (2). These orbitals take on a directional character [represented by (+ or dark shading) and (– or light shading)] when they are in close proximity to another atom, orbital, or polarized

species, as is the case in a covalent bond. There are, therefore, two possibilities when two sp^2 hybridized orbitals come together. Orbitals of the same sign can be directed toward each other, as in **3**, or orbitals of opposite sign can be directed toward each other, as in **4**. In **3**, the electron density between the two nuclei is maximized (electronic attraction for the positive nucleus), but in **4**, it is minimized. Since a strong covalent bond (mutual sharing of electron density

between nuclei) is associated with significant electron density between the nuclei, **3** represents a **bonding** interaction, and **4** is usually viewed as an **antibonding** interaction. These terms have meaning only when considering the outermost orbital containing electrons, the valence electrons (valence orbitals).



Figure 11.1. Bonding and Antibonding σ - and π -Orbitals.

Similar arguments can be made for the overlap of the p-orbitals that constitute a π bond. In 5, the overlap of orbitals with the same sign represents the maximum bonding interaction for the π -bond of ethylene (a bonding molecular orbital), and 6 represents an antibonding molecular orbital. As with a σ -bond, the net energy of the bonding interaction in a π bond is lower than that of the antibonding interaction, as shown in Figure 11.1, and it is more stable. The energy of each molecular orbital can be measured, and this energy difference (ΔE) will vary with substituents on the alkene. This observation has important implications for the reactivity of these compounds, and this concept will be discussed below.

The π -orbitals are the key to understanding pericyclic reactions, and we will focus on the π bond of alkenes and dienes in this section. The difference in energy between the two π molecular orbitals (5 and 6) can be represented in terms of their relative energies, as shown in Figure 11.1, taken from Houk's work.¹ The lowest energy orbital containing the bonding electrons is called the **highest occupied molecular orbital**, the **HOMO**. Experimentally, the energy of the HOMO is the **negative** of the **ionization potential** (**IP**) of the molecule.² In terms of chemical reactivity, the HOMO is the orbital that donates electrons, and the IP is a reasonable measure of its energy. The higher energy orbital does not contain electrons, but is the next available energy level if electrons are available. The energy that describes accepting electrons is the **electron affinity** (**EA**), and this orbital is called the **lowest unoccupied molecular orbital**, the **LUMO**. Experimentally, the energy of the LUMO is taken to be the **negative** of the EA of the alkene.^{1,2} *In a simplistic reaction model, the LUMO would be expected to accept electrons from the HOMO*

^{1.} Houk, K.N.; Sims, J.; Watts, C.R.; Luskus, L.J. J. Am. Chem. Soc. 1973, 95, 7301.

Houk, K.N. in *Pericyclic Reactions, Vol. II*, Marchand, A.P.; Lehr, R.E. (Eds.), Academic Press, New York, 1977, p. 203.

of another π bond. The difference in energy between the HOMO and LUMO (ΔE) is determined by the difference of the IP (-10.52 eV for ethene² where 1 eV = **electron volt** = 23.06 kcal mol⁻¹ = 96.53 kJ mol⁻¹), and the EA is +1.5 eV (for a ΔE of 12.02 eV = 277.2 kcal mol⁻¹ = 1160.4 kJ mol⁻¹).

The HOMO and LUMO of ethene (or of any other molecule) are referred to as **frontier molecular orbitals** (**FMO**), after the pioneering work of Fukui.³ Analyzing several different types of reactions with FMO theory, the HOMO was believed to deliver electrons to the LUMO of a reactive center that could accept the charge (as mentioned above). The FMO theory has now been shown to be "a first approximation to a perturbation treatment of chemical reactivity".⁴ Perturbation theory,⁵ as first described by Coulson and Longuet-Higgins,⁶ treats the molecular orbital of two interacting components as a perturbation of the product of their individual orbitals.⁷ *The theory fails to explain large perturbations, and does not predict the transition state, but gives "an estimation of the slope of an early part of the path along the reaction coordinate leading to the transition state, and this information is useful for predicting reactivity. The transition state energies can be described as reactant-like (early transition state) or product-like (late transition state). The well-known Hammond postulate states "that transition states for exothermic reactions are reactant-like, and for endothermic reactions are product-like".⁸ Frontier orbital effects are therefore particularly important in exothermic reactions.⁹*

Analysis of a reaction by frontier orbital theory has additional benefits, particularly for predicting reactivity and stereochemistry. Woodward and Hoffman¹⁰ pointed out "that electrocyclic reactions followed the stereochemistry dictated by the symmetry, or nodal properties of the HOMO of the polyene".¹¹ This concept of orbital symmetry will be important for discussions of all pericyclic reactions. Of particular importance is the difference in energy between the HOMO of one π system, and the LUMO of a second π -system, because this energy difference (ΔE) will be used to predict reactivity in pericyclic reactions (see below). A cautionary note was raised by Spino and co-worker's,¹² who showed that the HOMO_{diene}–LUMO_{alkene} values should be used with caution when attempting to predict inverse electron demand Diels-Alder

- 8. Hammond, G.S. J. Am. Chem. Soc. 1955, 77, 334.
- 9. Reference 7, p 24.

- 11. Reference 2, pp 183-184.
- 12. Spino, C.; Rezaei, H.; Dory, Y.L. J. Org. Chem. 2004, 69, 757.

 ⁽a) Fukui, K.; Yonezawa, T.; Nagata, C.; Shingu, H. J. Chem. Phys. 1954, 22, 1433; (b) Fukui, K. in Molecular Orbitals in Chemistry, Physics and Biology, Löwdin, P.-O.; Pullman, B. (Eds.), Academic Press, New York, 1964, p. 513.

^{4.} Reference 2, p 183.

 ⁽a) Dewar, M.J.S.; Dougherty, R.C. *The P.M.O. Theory of Organic Chemistry*, Plenum Press, New York, 1975; (b) Dewar, M.J.S. *Molecular Orbital Theory for Organic Chemists*, McGraw Hill, New York, 1969.

^{6.} Coulson, C.A.; Longuet-Higgins, H.C. Proc. Roy. Soc, A 1947, 192, 16.

^{7.} Fleming, I. Frontier Molecular Orbitals and Organic Chemical Reactions, Wiley, London, 1976, p 23.

^{10. (}a) Woodward, R.B.; Hoffman, R. Angew. Chem. Int. Ed. 1969, 8, 781; (b) Idem The Conservation of Orbital Symmetry, Verlag-Chemie GmbH/Academic Press, Weinheim, 1971.

reactions (see sec. 11.5), where the asynchronicity of the transition state should be taken into account. Orbital coefficients (see sec. 11.2.B) can be used to understand both reactivity and regiochemistry, however.¹³

11.2.B. HOMO, LUMO Energies and Orbital Coefficients

Figure 11.1 showed the molecular orbitals for ethylene, and these are shown again in Figure 11.2. The magnitude of each orbital, called the **orbital coefficient**, is now shown. The + and – signs correlate with the symmetry of the orbital,² which is somewhat arbitrary, but useful for examining the directionality of two reactive orbitals. When two π systems differ in their substitution pattern, there will be differences in the magnitude of orbital densities (larger or smaller orbitals). Predictions concerning reactivity must, therefore, indicate the magnitude of electron density in each orbital.



Figure 11.2. Changes in Alkene Homo and Lumo Energies Upon Introduction of Substituents.

The orbital coefficients in the HOMO of a symmetrical molecule such as ethene are identical in magnitude and sign. The LUMO coefficients are equal in magnitude but opposite in sign, also a result of this symmetry, and this leads to no node in **5**, and one node in **6** (a **node** is a *point of zero electron density* relative to the orbital lobes). The importance of orbital coefficients will be discussed in Section 11.4.C. Low energy orbitals are associated with a minimal number of nodes, and higher energy orbitals with increasing numbers of nodes. If we change the structure of ethene by replacing a hydrogen atom with an electron-withdrawing group, as is the case for methyl acrylate, electron density is distorted away from the π bond of the alkene, toward the carbonyl. This distortion will influence the energies of the HOMO and LUMO as well as the magnitude of the orbital coefficients. The energy of the HOMO of methyl acrylate is -10.72 eV and the LUMO energy is 0 eV.¹³ These energy values are lower than the frontier orbitals of ethene (see Figure 11.2), which is shown in Figure 11.2,² and the dashed line marks

^{13.} Reference 2, pp 203-205.

the energy of the LUMO of ethene as the reference point. The LUMO energy is affected to a greater extent than the HOMO energy. As seen in Figure 11.2, the electron-withdrawing group diminishes the size (orbital coefficient) of the orbitals closest (*proximal*) to the δ + carbonyl carbon, leaving the most distant (*distal*) orbital with the largest coefficient.

The opposite effect is expected when a hydrogen of ethene is replaced with an electron releasing group such as OMe, as is the case with methyl vinyl ether (see Figure 11.2). The oxygen atom releases electrons toward the π bond, raising the energy of the orbitals relative to ethene (to -9.05 eV for the HOMO and +2.0 eV for the LUMO).² In Figure 11.2,² the HOMO coefficients of the carbon proximal to the methoxy are diminished (0.39 vs. 0.61), whereas the orbital density of the distal carbon is increased. In the LUMO, however, the orbital on the proximal carbon is slightly larger than that on the distal carbon. In general, the HOMO coefficients for methyl vinyl ether are typical of other electron-releasing substituents, but the LUMO coefficients are often closer to each other in magnitude. Table 11.1 shows the HOMO and LUMO energies for several common alkenes, along with the HOMO and LUMO coefficients, where available.

	номо				MO	
Alkene	HOMO (eV)	<u>c1</u>	<u>c2</u>	LUMO (eV)	<u>c3</u>	<u>c4</u>
H ₂ C=CH ₂ ^a	-10.52	0.71 [.63]	0.71 [.63]	1.5	0.71 [.86]	-0.71 [.86]
H ₂ C=CHCl ^a	-10.15	0.44	0.30	0.5	0.67	-0.54
H ₂ CHMe ^a	-9.88	0.67	0.6	1.8 ^{a,b}	0.67	-0.65
MeHC=CHMe	-9.13 ^c	[61]	[61]	2.22 ^d	[78]	[.78]
EtHC=CH ₂	-9.63 ^e	[64]	[59]	2.01 ^e	[80]	[.80]
cyclohexene	-8.94 ^{f,g}	[60]	[60]	2.1 ^g	[79]	[.79]
H ₂ C=CHPh	-8.48	0.49[43]	0.32[29]	0.8	0.48[51]	-0.33[.35]
H2C=CHCH2OHa,d	-10.1	-0.31	-0.36	1.1	-0.64	-0.56
H ₂ C=CHOMe ^a	-9.05(-8.93) ^c	0.61[60]	0.39[42]	2.0	0.66[79]	-0.72[.83]
H ₂ C=CHOEt	-9.03 ^{a,c}			5.53 ^{a,c}		
$H_2C=C(OEt)_2$	-8.68 ^{a,c}			6.28 ^{a,c}		
H ₂ C=CHSMe ^a	-8.45	0.34	0.17	1.0	0.63	-0.48
H ₂ C=CHNMe ₂ ^a	-9.0	0.50	0.20	2.5	0.62	-0.69
H ₂ C=CHCO ₂ H ^b	-10.93	[49]	[47]	2.91	-0.63[65]	0.46[.47]
H ₂ C=CHCO ₂ Me	-10.72(-10.64) ^{a,c}	0.43	0.33	0(3.12) ^{a,c}	0.69	-0.47
MeO ₂ CHC=CHCO ₂ Me ^{a,d}	-10.95 ^{a,c}			1.94 ^{a,c}		
$H_2C=C(CO_2Et)_2$	-10.96 ^{a,c}			2.43 ^{a,c}		
H ₂ C=CHCHO	-10.89 ^b	0.58 ^a [59]	$0.48^{a}[-55]$	0.60 ^b	-0.58 ^b [62]	-0.40 ^b [.43]
H ₂ C=CHCHO•BF ₃ ^b	-12.49			0.43	-0.53	0.25
methyl vinyl ketone	-10.16 ^s	[10]	[18]		[61]	[.44]
cyclopentenone	-9.34 ^{c,q}	0.56 ^{a,b}	0.70 ^{a,b}	-0.64 ^q	$-0.74^{a,b}$	0.52 ^{a,b}

 Table 11.1
 HOMO and LUMO Energies and Orbital Coefficients of Common Alkenes

A 11		-1	-2		o ³	o.4
Aikene	10 20h	<u>CI</u>	<u>v2</u>	<u>LUMU (ev)</u>	<u>63</u>	<u>U4</u> [22]
<i>p</i> -benzoquinone	-10.29 th	[34]	[34]	-1.91	[55]	[.55]
maleic anhdyride	-11.95"(-12.13)",°	[34]	[34]	$-0.5/(1.03)^{a,c}$	[51]	[.51]
N-phenylmaleimide	-10.64°	[10]	[.10]	-0.49 ^r	[.46]	[46]
H ₂ C=CHCN	-10.92	$0.60(.64)^{a,b}$	0.49(0.6)	0 ^{a,0}	$0.68(.55)^{a,b}$	$-0.54(67)^{a,b}$
$H_2C=C(CN)_2^r$	-11.38	0.61	0.45	-1.54	0.66	-0.49
$(NC)_2C=C(CN)_2$	-11.8^{k}			$-1.80^{l}(-2.03)^{m}$		
H ₂ C=CHNO ₂ ^a	-11.4	0.62[.005]	0.60[002]	0.7	0.54[.50]	-0.32[.30]
HC=CH	-11.4 ^g	[62]	[62]	2.6 ^g	[86]	[.86]
MeC=CMe	-9.9 ^c			3.43 ⁿ		
HC=CCN ^r	-11.81	0.56	0.43	0	0.57	-0.41
MeO ₂ CC=CCO ₂ Me	-11.5 ^p	[.37]	[.37]	-0.60^{f}	[.42]	[42]
acetaldehydez	-11.49	0.44 ^{aa}		4.21	[.44]	[44]
thioacetaldehydez	-9.25	0.62 ^{aa}		1.81	0.64	-0.62[.09] ^u
phenanthrene (C9-C10)	-8.1 ^{c,q}	[37]	[.37]	-0.31 ^q	0.65	-0.66[.07] ^u
H ₂ C=C=CH ₂ ^t	-10.14	-0.47	$-0.56(.20)^{u}$	2.4	0.67	$-0.63(.10)^{u}$
H ₂ C=C=CMe ₂ ^t	-9.67	-0.66	$-0.63(.09)^{u}$	0.78	0.54	$-0.65(.05)^{u}$
H ₂ C=C=CHOMe ^t	-9.33	-0.53	$-0.63(.12)^{u}$	1.01	0.48	$-0.63(.04)^{u}$
H2C=C=CHCNt	-10.45	-0.63	$-0.55(.22)^{u}$	-0.01	0.22	0.57(.75) ^w
H ₂ C=C=CHCO ₂ Me ^t	-10.62	-0.67	$-0.53(.23)^{u}$	-0.07	-0.51	0.71(32) ^w
$H_2C=C=O^v$	$-12.55(-12.7)^{x}$	-0.73	$-0.27(.61)^{v}$	2.55	-0.16	$0.45(23)^{W}$
MeHC=C=O ^v	-11.52(-8.95) ^y	-0.67	-0.33(.55) ^w			
PhHC=C=O	$-10.61(-10.56)^{x}$	-0.53	-0.30(.43)			
Me ₂ C=C=O	-8.45 ^y		~ /			
CIHC=C=O	-9.24 ^y					
$Cl_2C=C=0$	-9 15 ^y					
NCHC=C=O	-10.07^{y}					
	10.07					

 Table 11.1
 HOMO and LUMO Energies and Orbital Coefficients of Common Alkenes (con't).

Values in [] calculated using MacSpartan, v2.0.2, Hartree-Fock calculations at STO-3G level. ^aAll data From Ref. 13 unless otherwise noted. ^b From Ref. ¹⁴. ^c From Ref. ¹⁵. ^d From Ref. ¹⁶. ^e From Ref. ¹⁷. ^f From Ref. ¹⁸. ^g From Ref. ²⁰. ⁱ From Ref. ²¹. ^j From Ref. ²². ^k From Ref. ²³. ¹ From Ref. ²⁴. ^m From Ref. ²⁵. ⁿ From Ref. ²⁵. ⁿ From Ref. ²⁶. ¹⁶ From Ref. ²⁶. ¹⁷ From Ref. ²⁶. ¹⁶ From Ref. ²⁶. ¹⁷ From Ref. ²⁶. ¹⁷ From Ref. ²⁶. ¹⁶ From Ref. ²⁶. ¹⁷ From Ref. ²⁶. ¹⁶ From Ref. ²⁶. ¹⁶ From Ref. ²⁷. ¹⁶ From Ref. ²⁸. ¹⁶ From Ref. ²⁸. ¹⁶ From Ref. ²⁹. ¹⁶ F

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- 25. Dewar, M.J.S.; Rzepa, H.S. J. Am. Chem. Soc. 1978, 100, 784.

Ref.²⁶. ^oFrom Ref.²⁷. ^pFrom Ref.²⁸. ^qFrom Ref.²⁹. ^rall data From Ref.³⁰. ^sFrom Ref.³¹. ^tall data From Ref.³². ^u third coefficient (C1 for CR₂; C2 for =C=; C3 for CH₂=); ^v all data From Ref.³³ unless otherwise noted. ^w third coefficient (C1 for RCH; C2 for =C=; C3 for =O). ^x From Ref.³⁴. ^y From Ref.³⁵ ^z From Ref.³⁶ ^{aa} Fror O=C, where C₁ is for O and C₂ is for C ^{ab} From Ref.³⁷; ^{ac} From Ref.³⁸; ^{ad} *trans*; ae From Ref.³⁹

The data in Table 11.1 came from a variety of sources, including calculations⁴⁰ and experimentally determined ionization potential and EA data. These numbers vary with the experimental method, and the sophistication level of the calculation. They should be viewed as useful first estimates when comparing ΔE 's using values from two different sources (and/or methods). Caution should be exercised. The purpose of this table is to use the HOMO-LUMO energies to predict chemical reactivity (*vide infra*, sec. 11.4.B). The orbital coefficients will be used to predict regioselectivity (*vide infra*, sec. 11.4.C.ii). When two or more electron-withdrawing groups are present (tetracyanoethylene, benzoquinone, maleic anhydride, etc.), greater lowering of the HOMO is apparent and the LUMO energy may fall below 0 eV. Ethyne is generally higher in energy than ethene, but electron-releasing and -withdrawing substituents have a similar effect (note -11.4 eV for acetylene vs. -11.5 eV for dimethyl acetylene dicarboxylate, pointing to the problems of using different methods to determine the ionization potential).

Data are also shown for allene and ketene derivatives, which react similarly to alkenes in pericyclic reactions. The HOMO and LUMO energies are generally lower than those of ethene and the orbital coefficients of interest are those at C2 and C3 in the LUMO of allenes and C1 and C2 in ketenes. As will be seen in Sections 11.4.B and 11.11, the LUMO energies and coefficients are important for predicting reactivity and selectivity in several types of pericyclic reactions.

As seen above, a conjugating substituent (C=O or C=N, Ph) lowers the energy of both the HOMO and the LUMO, and its presence also perturbs the orbital coefficients. Table 11.1 shows an entry for styrene in which the HOMO is higher in energy, but the LUMO is lower (relative to ethene), and this result is also seen in Figure 11.3. The orbital coefficients are smaller closest to the phenyl, and are significantly smaller in magnitude. These effects appear in dienes where

- 33. Meslin, J.C.; N'Guessan, Y.T.; Quiniou, H.; Tonnard, F. Tetrahedron 1975, 31, 2679.
- 34. Kuzuya, M.; Miyake, F.; Okuda, T. J. Chem. Soc. Perkin Trans. 2 1984, 1471.
- 35. Bock, H.; Hirabayashi, T.; Mohmand, S. Chem. Ber. 1981, 114, 2595.
- 36. Yu, Z.-X.; Wu, Y.-D. J. Org. Chem. 2003, 68, 412.
- 37. Suishu, T.; Shimo, T.; Somekawa, K. Tetrahedron 1997, 53, 3545.
- 38. Spino, C.; Rezaei, H.; Dory, Y.L. J. Org. Chem. 2004, 69, 757.
- 39. Yoshitake, Y.; Yamaguchi, K.; Kai, C.; Akiyama, T.; Handa, C.; Jikyo, T.; Harano, K. J. Org. Chem. 2001, 66, 8902.
- 40. Using MacSpartan, v.2.0.2, Wavefunction, Inc., Irvine, CA.

^{26.} Ng, L.; Jordan, K.D.; Krebs, A.; Rüger, W. J. Am. Chem. Soc. 1982, 104, 7414.

^{27.} El-Basil, S.; Said, M. Ind. J. Chem. 1980, 19B, 1071.

^{28.} Bihlmaier, W.; Huisgen, R.; Reissig, H.-U.; Voss, S. Tetrahedron Lett. 1979, 2621.

^{29.} Michl, J.; Becker, R.J. J. Chem. Phys. 1976, 46, 3889.

^{30.} Houk, K.N. Acc. Chem. Res. 1975, 8, 361.

^{31.} Hentrich, G.; Gunkel, E.; Klessinger, M. J. Mol. Struct., 1974, 21, 231.

^{32.} Padwa, A.; Bullock, W.H.; Kline, D.N.; Perumattam, J. J. Org. Chem. 1989, 54, 2862.

the conjugating substituent is another ethene moiety (1,3-butadiene, for example). In Figure 11.3, the HOMO energy for butadiene is -9.03 eV (with coefficients of 0.57 and 0.41). The LUMO energy is lowered to +1.0 eV with coefficients of 0.56 and -0.42, relative to ethene,⁴¹ which is a net electron-withdrawing effect, but the influence of the HOMO and LUMO is similar to the effects noted for styrene.



Figure 11.3. Influence of a Conjugating Substituent on Alkene Homo and Lumo Energies.

In Figure 11.3, 1,3-butadiene is treated as a substituted alkene, which is a contrivance used to illustrate the significant interaction of the conjugated π system, as reflected in the HOMO and LUMO energies. Although the HOMO-LUMO coefficients for all four atoms of the conjugated system must be considered, only those at the termini will interact with the alkene in a Diels-Alder reaction. 1,3-Butadiene is symmetrical, and the coefficients reflect not only the equal distribution of electron density in the orbitals (see Figure 11.3), but also the electron withdrawing effect invoked in Figure 11.3. The largest concentration of electron density occurs at the terminal carbons, and these are expected to be the major sites of reactivity. In butadiene, there are four π orbitals and four π electrons, so there are four molecular orbitals as shown. The HOMO and LUMO energy levels in Figure 11.4⁴¹ are only two of four frontier orbitals. The lowest energy orbital has no node, the HOMO has one node, the LUMO has two nodes, and the highest energy orbitals has three nodes. The orbitals are shown using a convenient drawing convention with p-orbitals at each carbon. Orbital pictures calculated with MacSpartan are also shown for the HOMO and LUMO.²⁴ In this diagram, the two lowest energy orbitals contain electrons, with the HOMO being the higher of the two. For analysis of cycloaddition reactions, the HOMO will be more important than the other orbitals, since it contains electrons that can be donated. Similarly, the LUMO is the lowest energy of the unfilled orbitals, and is more important for reactions since it will preferentially accept electrons. For dienes, attention will be focused entirely on the HOMO and LUMO.

^{41.} Reference 2, p 204.



Figure 11.4. Orbital Diagram for 1,3-Butadiene.

When substituents are attached to a diene, effects on the frontier orbitals are similar to those observed with alkenes. Electron withdrawing groups decrease the energy of the HOMO and LUMO relative to butadiene, and electron releasing groups increase the HOMO and LUMO energies. There is a new problem of regiochemistry, however, since the substituent can be attached to C1 or C2 of the diene. The Z group is a generic electron-withdrawing group, and the X group is a generic electron-releasing group, as used by Fleming⁴² and Houk.⁴³ The energies for the HOMO and LUMO are mostly taken from the work of Houk.⁴³ As expected, the electron withdrawing groups lower the HOMO and the LUMO (see Figure 11.5).⁴³ The C1 substituent lowers the energy more than a C2 substituent and the orbital coefficients are larger on the orbitals distal to the Z group for C1 substituents, although they are larger on the proximal carbon for C2 substituents. The orbital on the carbon distal to the X group is smallest for C1 substituents, and largest for C2 substituents in the LUMO. In the HOMO, the orbital on the carbon distal to the Z group attached to C1 is largest for the HOMO, and smallest for the LUMO, which is reversed when the Z group is attached to C2 (see Figure 11.5). Orbital coefficients are largest for C2 substituents in the LUMO. Typical substituted dienes are presented in Table 11.2, along with the HOMO and LUMO values and the available coefficients.

^{42.} Reference 7, p 128.

^{43.} Houk, K.N. J. Am. Chem. Soc. 1973, 95, 4092.



Figure 11.5. Relative Homo and Lumo Energies of Electron-Rich and Electron-Poor Dienes.

[Reprinted with permission from Fleming, I. Frontier Molecular Orbitals and Organic Chemical Reactions, Wiley, London, 1976, p. 128. Copyright © 1976 by John Wiley and Sons, Inc.]

As with the energy levels and coefficients presented in Table 11.1, the values in Table 11.2 vary with the experimental method used to obtain them, and with the sophistication level of the calculation. Two HOMO and LUMO values are given for butadiene to illustrate this. It is clear, however, that the electron-releasing and -withdrawing effects are as predicted. Cyclopentadiene is interesting in that it shows significant lowering of the LUMO, as does cyclohexadiene relative to butadiene, and especially relative to the acyclic 2,4-pentadiene. Introduction of an electron-releasing heteroatom in the ring (furan, thiophene, and pyrrole) leads to a LUMO of lower energy relative to methoxy or methylthiobutadiene, but the LUMOs are higher in energy than cyclo-pentadiene. The HOMO energies (as well as the c_1 and c_2 orbital coefficients) will prove useful for analyzing Diels-Alder and [3+2]-cycloaddition reactions.

	R^{2} $R^{1} \bigoplus_{C_{1}}$		МО	R^{2} $R^{1} \bigoplus_{c_{3}} c_{4}$	LUMO	
<u>Diene</u>	HOMO (eV)	<u>c1</u>	<u>c2</u>	LUMO (eV)	<u>c3</u>	<u>c4</u>
a a	-9.07(-8.85) ^b	0.57	-0.57	1.0(3.38) ^b	0.56	0.56
Me — b	-9.78 ^a (-8.54)	0.314	0.315	3.51	0.629 ^c	0.617 ^c
Me ^b	-8.81°					
Me b	-9.04a(-8.72)	0.340	0.296	3.38	0.56 ^d	0.55 ^d

 Table 11.2
 HOMO, LUMO Energies and Orbital Coefficients for Substituted Dienes

<u>Diene</u>	HOMO (eV)	<u>c1</u>	<u>c2</u>	LUMO (eV)	<u>c3</u>	<u>c4</u>
Me Me	-8.76 ^a (-8.62) ^o			2.18 ^e		
Me Me	-8.39 ^a (-8.09) ^o					
Ph _/	-8.16 ^{a,o}	0.408^{f}	0.416 ^f			
Ph	-8.38°					
PhPh	-8.09°					
Ph	-8.77 ^{a,o}	0.572 ^g	0.335 ^g			
MeO -	$-8.21^{a,o}(-8.24)^{b}$	0.235 ^b	0.313 ^b	3.77 ^b	0.644 ^c	0.609 ^c
OMe	-8.62 ^{a,o}	0.352 ^b	0.103 ^b	3.60 ^b		
MeO PhS	-9.94 ^p	-0.296 ^p	0.231 ^p	2.41 ^p	-0.399 ^p	-0.502 ^p
MeO SPh	-10.50 ^p	-0.079 ^p	0.329 ^p	2.18 ^p	-0.431 ^p	-0.615 ^p
SMe	-7.94	0.24-	0.256	3.25		
MeS b	-8.37	0.399	0.201	3.25		
CO ₂ H	-9.41 ^b	0.483 ^f	0.460 ^f	1.99 ^b		
CO ₂ H b	-9.24	0.279	0.326	2.39		
^b C≡N	-9.45			1.86		
KC≡N b	-9.58	0.595 ^g	0.490 ^g	2.12		
\bigcirc	-8.97 ^h (-8.58) ^o			0.75 ⁱ		
\bigcirc	-8.2 ^{j,k}			0.73 ^k (0.80) ^{j,1}		
N N	-8.2 ^{h,m}			2.38 ^{l,n}		
	-8.8 ^{h,m}			1.76 ^{l,n}		
$\langle s \rangle$	-8.9 ^{h,m}			1.17 ^{l,n}		

 Table 11.2
 HOMO, LUMO Energies and Orbital Coefficients for Substituted Dienes, (con't).

^a taken from Ref.⁴⁴ unless otherwise noted. ^b taken from Ref. 13 unless otherwise noted. ^c from Ref.⁴⁵. ^d from Ref. 29. ^e from Ref.⁴⁶. ^f from Ref.⁴⁷. ^g from Ref.⁴⁸ ^h from Ref. 14. ⁱ from Ref. 17. ^j from Refs. 15,⁴⁹. ^k from Ref.⁵⁰. ¹ from Ref.⁵¹. ^m from Ref.⁵². ⁿ from Ref.⁵³ ^o from Ref.⁵⁴ ^p from Ref.⁵⁵

11.3. ALLOWED AND FORBIDDEN REACTIONS

Most of the reactions involving multiple π bonds can be classified by the number of π -electrons in each reaction partner. A single π bond (2 π electrons) can interact with another single π bond of an alkene or a diene (2 more π electrons). The reaction of two alkenes (see Figure 11.6) is therefore classified as a $2\pi + 2\pi$ reaction. When a diene with four π electrons reacts with an alkene having two π electrons (Figure 11.6), there are a total of 6 π electrons and this is a 4 π + 2π reaction. Reaction of an allyl anion with an alkene (Figure 11.6) is classified as a $3\pi + 2\pi$ reaction, and is a simple example of the so-called dipolar addition discussed in Section 11.11. Woodward and Hoffman^{10b,56} correlated each reaction type with the symmetry of their frontier orbitals, allowing predictions to be made concerning their reactivity. They classified reactions as allowed or forbidden. In an allowed reaction, a four-center transition state is stabilized more than a two-center transition state; in a forbidden reaction, vice versa. For reaction of a diene and an alkene (see Figure 11.6), the four-center transition state is represented by 7 and the two-center transition state by 8.57 This problem can be further defined in terms of the number of π electrons in the polyene. In 4 n + 2 n π systems (*n* = the number of π -electrons), the 4 π -electrons in 1,3-butadiene, for example, react with the 2 π electrons of an alkene. The HOMO of the diene contains terminal atoms with orbitals of opposing symmetry (HOMO_{diene} in 7) and the orbital coefficients have opposite signs,⁵⁸ which contrasts with a 4n π electron system (n = 0, 1, 2, 3, ..., with 0, 4, 8, 12, ..., π electrons, such as the 2 π -electrons of one alkene reacting with the 2 π electrons of a carbonyl π bond). The HOMO contains orbitals of the same symmetry and sign in symmetrical alkenes, but the LUMO contains orbitals of

56. Hoffmann, R.; Woodward, R.B. J. Am. Chem. Soc. 1965, 87, 2046.

^{44.} Sustmann, R.; Schubert, R. Tetrahedron Lett. 1972, 2739.

^{45.} Kakushima, M. Can. J. Chem. 1979, 57, 2564.

^{46.} Kroner, J.; Bock, H. Theoret. Chim. Acta 1968, 12, 214.

^{47.} Alston, P.V.; Ottenbrite, R.M.; Shillady, D.D. J. Org. Chem. 1973, 38, 4075.

^{48.} Alston, P.V.; Ottenbrite, R.M. J. Org. Chem. 1975, 40, 1111.

^{49.} Jordan, K.D.; Burrow, P.D. Chem. Phys. Lett. 1975, 36, 594.

^{50.} Giordan, J.C.; McMillan, M.R.; Moore, J.H.; Staley, S.W. J. Am. Chem. Soc. 1980, 102, 4870.

^{51.} Jordan, K.D.; Burrow, P.D. Acc. Chem. Res. 1978, 11, 341.

^{52.} Lazzaroni, R.; Boutique, J.P.; Riga, J.; Verbist, J.J.; Fripiat, J.G.; Delhalle, J.J. Chem. Soc. Perkin Trans. 21985, 97.

^{53.} Van Veen, E.H. Chem. Phys. Lett. 1976, 41, 535.

^{54.} Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. Chem. Ber. 1980, 113, 1663.

^{55.} Alston, P.V.; Gordon, M.D.; Ottenbrite, R.M.; Cohen, T. J. Org. Chem. 1983, 48, 5051.

^{57.} Reference 2, p 216.

^{58.} Reference 2, p 209.

opposing symmetry and sign (see LUMO_{alkene} in 7). The symmetry of the alkene LUMO is the same as that found in the HOMO of the diene. In a reaction, maximum stability in the transition state is observed when the terminal carbons of the HOMO_{diene} interact with the termini of the LUMO_{alkene}. These orbitals have the same symmetry and such interactions are allowed. If the orbitals have the opposite symmetry (and sign) the interaction is forbidden.⁵⁹



Figure 11.6. Common Pericyclic [m+n] Reactions.

Woodward and Hoffman described addition modes, based on the facial approach of the reactive termini, as **suprafacial** and **antarafacial**.⁶⁰ "A suprafacial process is one in which bonds made or broken lie on the same face of the system undergoing reaction", as in 9.⁶⁰ An antarafacial process has the "newly formed or broken bonds on opposite sides of the reaction system," as in 10.⁶⁰ Woodward and Hoffman then described several specific π interactions, and classified



them as symmetry allowed or symmetry forbidden (the so-called Woodward-Hoffman rules). Each π process could then be assigned an *s* (suprafacial) or an *a* (antarafacial) to describe the facial approach of the reactive termini. Lehr and Marchand use addition of bromine to *cis*-2-butene to illustrate these modes of addition.⁶¹ Antarafacial addition leads to the *d*,*l*-dibromide (11), whereas a suprafacial addition would give the meso-dibromide (12). These modes of addition for electrocyclic reactions will be further illustrated in later discussions (see 11.11).



- 59. Reference 2, p 210.
- 60. Reference 10b, p 65.

^{61.} Lehr, R.E.; Marchand, A.P. Orbital Symmetry, Academic Press, New York, 1972, p 16.

Finally, it is imperative that we categorize the energy source used to effect the reaction as either heat (a thermal reaction) or light (a photochemical reaction - sec. 11.10.B is a brief introduction to photochemistry). The lowest energy arrangement of electrons (shown in **13** for an alkene) is referred to as the **ground state**. If this orbital is used for reaction, the HOMO will react with an orbital of like symmetry, but the reaction does not require promotion of



an electron to the LUMO. This type of reaction only requires heating, since absorption of a photon of light will promote an electron to the antibonding orbital (convert $13 \rightarrow 14$). If the alkene reacts photochemically, a singly occupied molecular orbital (a SOMO) is formed, represented by 14, and it is the reactive orbital. Under thermal conditions, the ground state HOMO will dominate. If, however, the HOMO cannot react, heating will not affect the desired reaction, and it will occur only under photochemical conditions where an electron is promoted to the higher energy SOMO. It is, therefore, possible to characterize reactions as thermally allowed or forbidden, and as photochemically allowed or forbidden.

With these tools in hand, the **Woodward-Hoffman rules** of cycloaddition describe two π systems of $m \pi$ and $n \pi$ electrons. With these rules, 4 q and 4 q+2 systems (q = 0, 1, 2, 3,...) are classified as thermally and photochemically allowed or forbidden, as presented in Table 11.3.⁶² "For suprafacial interactions, the thermally allowed reactions involve one 4 q + 2 molecule and one 4 q molecule"¹⁰ [an alkene (q = 1 for 4q) and butadiene (q = 1 for 4 q + 2)]. "This gives a total of (4 q+2) π -electrons and the reaction is allowed. Forbidden reactions involve two 4 q or two 4 q+2 systems for a total of $4 n \pi$ electrons".¹⁰ In the following section, the three major types of cycloaddition reactions shown in Figure 11.6 will be examined. In Figure 11.6, the [4+2]-cycloaddition (4 n + 2 n) is thermally allowed, the [2+2]-cycloaddition is photochemically allowed and the [3+2]-cycloaddition is thermally allowed (although it is a 3 n + 2 n reaction).

Table 11.3.	Rules for	[m+n]	Cyclo	oadditions
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[<u>m + n]</u>	Allowed (ground state, thermal) <u>Forbidden (excited state, hv)</u>	Forbidden (ground state, thermal) <u>Allowed (excited state, hv)</u>
4q	$m_s + n_a m_a + n_s$	$m_s + n_s$ $m_s + n_a$
4 <i>q</i> + 2	$m_s + n_s$ $m_a + n_a$	$m_s + n_a$ $m_a + n_s$

^{62.} Reference 10b, p 70.

11.4. [4 + 2]-CYCLOADDITIONS

11.4.A. The Diels-Alder Reaction

In 1906, Albrecht reported a thermal reaction between cyclopentadiene and *p*-benzoquinone that gave a dimeric complex, later identified to be the [4+2]-cycloadduct, **15**.⁶³ In 1928, Diels and Alder reported this reaction, along with those of several dienes and alkenes, including maleic anhydride and



acrolein, and characterized the products.^{64,68} From these initial reactions, countless variations have been reported, and this has become one of the most important methods for constructing molecules in all of organic chemistry. This thermal reaction of a diene and an alkene (or other two π -electron system, generically known as a **dienophile**) is now called the **Diels-Alder reaction**.^{65,66} Diels and Alder were awarded the Nobel Prize for this reaction in 1950. The reaction is explained in terms of molecular orbital theory, and is recognized as a [4 n + 2 n]-cycloaddition reaction. In Section 11.3, a [4+2]-reaction was shown to be thermally allowed, and Figure 11.7 shows that the C1 and C4 orbitals of the HOMO of butadiene have the same symmetry as the orbitals of the LUMO of ethene. The reaction proceeds thermally, presumably by donation of electrons from the HOMO_{diene} to the LUMO_{alkene}. Orbitals of the same symmetry (see 7) react with transfer of electrons in a six-center transition state (**16**) to form two σ bonds and a new π bond in the cyclohexene product (**17**), as shown in Figure 11.8.



Figure 11.7. HOMO_{butadiene}-LUMO_{ethene} Interactions That Control the Diels-Alder Cyclization.

^{63.} Albrecht, W. Annalen 1906, 348, 31.

 ⁽a) Diels, O.; Alder, K.; Lübbert, W., Naujoks, E.; Querberitz, F.; Röhl, K.; Segeberg, H. Annalen 1929, 470, 62; (b) Diels, O.; Alder, K. Ber. 1929, 62, 2081; (c) Idem Ibid. 1929, 62, 2087.

^{65.} Larock, R.C. Comprehensive Organic Transformations, 2nd Ed., Wiley-VCH, New York, 1999, pp 523-544.

^{66. (}a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-2624 (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 206-209.



Figure 11.8. The Diels-Alder Reaction of Butadiene and Ethene.

The terminal orbitals in the *cisoid* conformation (sec. 1.5.A) bear the proper symmetry for reaction with the alkene, and only in this conformation can the HOMO orbitals come within bonding

distance of the LUMO orbital of the alkene. Acyclic dienes are in a dynamic equilibrium consisting of both cisoid (**18c**) and transoid (**18t**) conformations, but the lower energy transoid conformation is the major one. The equilibrium



mixture can be used because as the cisoid conformation reacts with the alkene, the equilibrium is shifted to give more cisoid as the reaction proceeds. If a diene is locked into a transoid geometry, as in 19, the Diels-Alder reaction does not occur. If the diene is locked into the cisoid form, as in cyclopentadiene (20), the reaction is expected to proceed faster. It is important to point out that this simple analysis ignores any steric interaction between diene and dienophile.

Substituents on the diene can increase the energy barrier to the cisoid form, which diminishes the rate of the Diels-Alder reaction. Attempts to react 2-methyl-2,4-pentadiene (**21**) with maleic anhydride at ambient temperature gave no reaction. The more reactive alkene tetracyanoethylene (TCNE, **22**) gave 11% of **23** in 20 h, but the major product was the [2+2]-cycloaddition product (**24**, sec. 11.10) in 69%.⁶⁷ This poor reactivity was attributed to the energy barrier required for **21** to assume a cisoid conformation.



67. Stewart Jr., C.A. J. Am. Chem. Soc. 1962, 84, 117.

11.4.B. Reactivity in the Diels-Alder Reaction

Diels-Alder reactions of cyclopentadiene with different alkenes proceed at different rates. Cyclopentadiene reacts with acrolein (25) in ether at room temperature (24 h) to give a 95% yield of 27.⁶⁸ This contrasts with the reaction of cyclopentadiene and ethene in ether to give a 74% yield of norbornene (28), which required heating to 200°C in an autoclave at 5800 psi pressure or 32 h. The presence of an electron releasing



group on the alkene causes the reaction to proceed with greater difficulty. Vinyl acetate (26) reacted with cyclopentadiene at 190°C in an autoclave (10 h, neat) to give only 25% of 29.

Generally, simple alkenes and electron-rich alkenes (bearing an electron-releasing group) will react with butadiene or cyclopentadiene only under very vigorous conditions. Molecular orbital theory explains these results by comparing the relative energy levels of the HOMO and LUMOs. If we use butadiene as an example (shown in Figure 11.9), the HOMO_{diene}-LUMO_{alkene} energy difference (ΔE) is 9.07 eV (209.15 kcal mol⁻¹, 875.5 kJ mol⁻¹) for a reaction between butadiene and ethyl acrylate. The ΔE for ethene-butadiene is 10.57 eV (243.74 kcal mol⁻¹, 1020.3 kJ mol⁻¹) and 11.07 eV (255.27 kcal mol⁻¹, 1068.6 kJ mol⁻¹) for methyl vinyl etherbutadiene. The smaller ΔE for ethyl acrylate is associated with a faster reaction.⁶⁹ These energy effects are correlated with the energy expression [Equation (11.1)]⁷⁰ derived by Klopman⁷¹ and Salem⁷² from perturbation theory. Fleming noted that the energy separation term of the HOMO and LUMO (E_r-E_s) is in the denominator of the equation, and a larger energy gap will slow the overall reaction.⁷⁰ The equation is

$$\Delta E = -\sum (q_a + q_b) \beta_{ab} S_{ab} + \sum_{k \le 1} \frac{Q_k Q_l}{e_R k_1} + \sum_r \sum_{s} -\sum_r \sum_{s} \sum_r \frac{2 (\Sigma_{ab} c_{ra} c_{sb} \beta_{ab})^2}{E_r - E_s}$$
 11.1

where q_a and q_b are electron populations of atomic orbitals *a* and *b*; β and *S* are the resonance and overlap integrals, respectively; the energy of the bonding orbital is

$$E_r = \frac{\alpha_1 + \beta}{1 + S} \qquad 11.2$$

- 71. Klopman, G. J. Am. Chem. Soc. 1968, 90, 223.
- 72. Salem, L. J. Am. Chem. Soc. 1968, 90, 543, 553.

^{68.} Diels, O.; Alder, K. Annalen 1928, 460, 98.

^{69.} Reference 7, pp 114-121.

^{70.} Reference 7, p 27.

and the energy of the antibonding orbital is



Figure 11.9. HOMO_{diene}-LUMO_{alkene} Interactions of Butadiene and Representative Alkenes

The first term in Equation 11.1 is the Coulomb integral,^{72b} and Q_k and Q_1 are the total charges on atoms k and l; e is the local dielectric constant; R_{k1} is the distance between atoms k and l; C_{ra} is the coefficient of atomic orbitals (a) in molecular orbital (r), where r refers to the molecular orbitals on one molecule and s refers to those on the other; and E_r and E_s are the energies of the molecular orbitals.

A comparison of ΔE for the HOMO_{diene} and LUMO_{alkene} of electron rich dienes and electron poor dienes upon reaction with ethyl acrylate (see Figure 11.9), shows that ΔE is smaller for electron rich dienes. For example, 1-ethoxy-butadiene reacts faster than ethyl 1,3-pentadienoate. A similar trend is observed with ethene and methyl vinyl ether, but the overall trend that the diene reacts faster with the electron poorer alkene is retained, as observed in the reaction of 1,3-butadiene with *trans*-cinnamic acid to give **30**, which required heating to 140°C for 20 h.⁷³ Similar reaction with 2-ethoxy⁻¹,3-butadiene gave a mixture of two cycloadducts after heating to 170°C for 48 h in an autoclave, but **31** was the major product.⁷⁴ The reaction of maleic anhydride and tetracyanoethylene showed similar reactivity.⁷⁵

^{73.} Alder, K.; Vagt, H. Vogt, W. Annalen 1949, 565, 135.

^{74.} House, H.O.; Gannon, W.F.; Ro, R.S.; Wluka, D.J. J. Am. Chem. Soc. 1960, 82, 1463.

^{75. (}a) Sustmann, R.; Schubert, R. Angew. Chem. Int. Ed. 1972, 11, 840; (b) see Reference 7, p 113.
Electron-releasing or -withdrawing substituents have a significant effect on the reactivity of the diene. Comparing the reaction of cyclopentadiene and acrolein to give **25** with cyclopentadiene and vinyl acetate to give **27** illustrates this point. Substituent effects on the HOMO of the diene will increase or decrease the HOMO_{diene}-LUMO_{alkene} interaction (ΔE). Electron-withdrawing groups will lower the HOMO of the diene and electron-releasing groups will raise the LUMO of the diene.

The conclusions drawn from these analyses show that the HOMO_{diene}-LUMO_{alkene} ΔE correctly predicts the *relative* reactivity of a given diene with a variety of alkenes, or of an alkene with a variety of dienes. As seen above, cyclopentadiene reacted faster with ethyl acrylate and slowest with methyl vinyl ether. The HOMO of cyclopentadiene is -9.87 eV (Table 11.2), the LUMO of methyl acrylate is 0 eV, and the LUMO of methyl vinyl ether is +2.0 eV (Table 11.1). The ΔE for methyl acrylate and cyclopentadiene is 9.87 eV, but the ΔE for methyl vinyl ether and cyclopentadiene is 11.87 eV. Methyl acrylate is expected to react faster. In general, alkenes with electron-withdrawing substituents react faster than alkenes with electron releasing substituents. This point is illustrated in Woodward's synthesis of reserpine, which began with the Diels-Alder reaction of benzoquinone **32** and 1,3-butadiene, to give **33** in 86%.⁷⁶



Reaction occurred preferentially at the double bond bearing the methyl group rather than at the more electron-rich vinyl ether. The HOMO_{diene}-LUMO_{alkene} ΔE for the methoxy side is larger than that for the methyl side, and butadiene reacted preferentially with the methyl side rather than the methoxy side. The Diels-Alder reaction forms two bonds in a single reaction and from a retrosynthetic standpoint, the two-bond disconnection for the Diels-Alder reaction is



76. Woodward, R.B.; Bader, F.E.; Bickel, H.; Frey, A.J.; Kierstead, R.W. Tetrahedron 1958, 2, 1.



To conclude this section, it is important to note that alkenes are not the only hydrocarbon dienophiles that are useful partners in the Diels-Alder reaction. Heterocyclic compounds, alkynes and even benzyne

are quite useful. In a synthesis of *epi*-zephyranthine by Padwa and Wang⁷⁷ an intramolecular Diels-Alder reaction of the alkene unit with the furan ring **34** gave a 55% yield of **35**. A benzyne derivative of pyridine was shown to undergo Diels-Alder reactions.⁷⁸ When 3-chloro-2-methoxypyridine (**36**) was treated with *tert*-butyllithium in THF at -78° C and then with furan, for example, cycloadduct **39** was obtained in 74% yield. The reaction is believed to proceed by aryl lithiation to give **37**, which loses LiCl to give the benzyne, **38**, which traps furan in a Diels-Alder reaction to give **39**.



Note that an alternative explanation has been presented, based on the relative position of the diene and the dienophile in the electrophilicity scale.⁷⁹ This analysis led to characterization of the HOMO_{Nu} – $LUMO_{E^+}$ interactions along a polar DA reaction and characterization of what the authors believe is a more favorable, two-center interaction along an asynchronous bond-formation process.

The **Arrhenius equation** indicates that the rate of a reaction depends on its activation energy, which is the difference in energy between the reactants and the transition state. The Arrhenius equation is

$$\begin{bmatrix} \text{rate} = k [A]^{a} [B]^{b} \end{bmatrix} \text{ and } k = Ae^{-\frac{E_{A}}{RT}} \text{ or } \ln k = \ln A - \frac{E_{A}}{RT}$$

where rate is in mol dm⁻³s⁻¹, k is the rate constant, [A] and [B] are concentrations in mol dm⁻³, the superscript a is the order of the reaction with respect to A and the superscript b is the order of the reaction with respect to B. The rate constant k is calculated as shown, where A is the frequency factor (pre-exponential factor), E_a is the activation energy in J mol⁻¹ (not kJ mol⁻¹), R is the gas constant and T is the temperature in Kelvin. All other factors being equal, the lower the activation energy the faster the reaction, but the Arrhenius equation is most successful for comparisons of closely related reactions. A Diels-Alder cycloaddition of different dienophiles with a common diene, for example, should lend itself to such a rate analysis.

^{77.} Wang, Q.; Padwa, A.. Org. Lett. 2004, 6, 2189.

^{78.} Connon, S.J.; Hegarty, A.F. J. Chem. Soc. Perkin Trans. 1 2000, 1245.

^{79.} Domingo, L.R. Eur. J. Org. Chem. 2004, 4788.

MOLECULAR MODELING: HOMO-LUMO Gaps and the Rates of Diels-Alder Reactions

Diels-Alder cycloaddition reactions most commonly involve electron-rich dienes and electrondeficient dienophiles (usually alkenes). According to the Frontier Molecular Orbital (FMO) model, the reaction is driven by the interaction of the most available occupied and unoccupied molecular orbitals. Specifically, electron transfer from the highest-occupied molecular orbital (HOMO) on the diene to the lowest-unoccupied molecular orbital (LUMO) on the dienophile stabilizes the transition state. This implies that the smaller the HOMO-LUMO gap, the faster will be the reaction. Therefore, it is reasonable to expect that the energy difference between HOMO of the diene and LUMO of the dienophile will relate to the activation energy for the reaction. While the HOMO and LUMO energies (and the HOMO-LUMO gap) cannot be measured (orbitals are not "real"), both are closely related to quantities that can be. Specifically, the HOMO energy is related to the ionization potential (the higher the energy of the orbital, the easier it is to expel an electron), and the LUMO energy is related to the electron affinity (the lower the energy of the orbital, the easier it is to capture an electron).

Build cyclopentadiene (the diene) and calculate the HOMO energy using the molecular orbitals menu item. Build each of the alkenes listed in the table (dienophiles), and calculate its LUMO energy. After the first calculation, *click* on > at the right of the tab at the top of the screen and select **Continue**. This will bring up a fresh builder palette while keeping this text on screen.

<u>Dienophile</u>	<u>log Relative Rate</u>
acrylonitrile	0
trans-1,2-dicyanoethylene	1.89
cis-1,2-dicyanoethylene	1.94
1,1-dicyanoethylene	4.64
tricyanoethylene	5.66
tetracyanoethylene	7.62

You can't make plots with *SpartanModel*, although you can with *Spartan Student* or *Spartan*. Use an external graphing program (or graph paper) to make a plot of the HOMO-LUMO gap ($E_{LUMO} - E_{HOMO}$) vs. the log of the rate of Diels-Alder cycloaddition reactions between cyclopentadiene and each of the dienophiles (tabulated above as relative to the log of the rate for reaction of cyclopentadiene and acrylonitrile). Does a decrease in HOMO-LUMO gap lead to a corresponding increase in reaction rate?

Optional: Try to identify a common diene with a HOMO energy that is higher (more positive) than the HOMO energy of cyclopentadiene. Try to identify a common dienophile with a LUMO energy that is lower (less positive) than the LUMO energy of tetracyanoethylene. Calcualate the HOMO-LUMO gap and, based on the correlation obtained above, predict a log of the rate of cycloaddition (relative to that of cyclopentadiene and acrylonitrile).

There is an alternative way to look at differences in rate of a Diels-Alder reaction. The most common Diels-Alder reactions are between electron rich dienes and electron-deficient dienophiles, for example, between cyclopentadiene and methyl vinyl ether or acrolein. This fact suggests that (negative) charge may be transferred from the diene to the dienophile, and may contribute to what is driving the reaction.

MOLECULAR MODELING: Geometries of Transition States and the Hammond Postulate

The energy required to reach the transition state in a reaction is known as the activation energy, E_{act} . Organic chemists, therefore, think of a transition state as being "at the top" of the pathway commonly referred to as a "reaction coordinate" connecting reactants and products. In part, this is true. A transition state is an energy maximum along the reaction coordinate. However, a chemical reaction where the reactant contains N atoms actually involves movement over an energy surface with 3N-6 dimensions, and a transition state is actually an energy minimum in each of the remaining (3N-7) dimensions. Liken a chemical reaction to a drive across a mountain range. The "goal" is to go from one valley to another, just as the goal of a chemical reaction is to go from one minimum on the energy surface (the reactants) to another minimum (the product). The road moves about a two-dimensional surface whereas the energy surface for a chemical reaction may involve dozens or even hundreds of dimensions. *There is no need to climb to the top of a mountain (a maximum in both dimensions) to go from one valley to another. Rather, is sufficient to go through a pass between mountains (a maximum in one dimension but a minimum in the other). Similarly, it is only necessary to pass through an energy maximum in one coordinate (the reaction coordinate) for a chemical reaction.*

Because a transition state is an energy maximum (albeit only in one of many dimensions) it cannot function to "trap" a molecule, let alone collect a population of "trapped" molecules. *This means that a transition state cannot even be observed experimentally let alone isolated or characterized. Quite simply, a transition state does not exist in the sense that a molecule exists.* However, it is possible to calculate the geometry and other properties of a transition state and to verify that in fact it is on a pathway connecting reactants and product. We shall refer to this as *transition state modeling.*

It is not possible to actually draw a multi-dimensional energy surface, and locating a transition state relies on its mathematical description. Reactants, products and transition states are so-called stationary points on an energy surface, that is, locations for which the first derivative of the energy with respect to each and every coordinate is zero. Think of them as points on the surface where the energy is neither heading up or down but rather is "flat". While the vast majority of stationary points have no "chemical meaning", there are two classes of points that are of interest. The *first* are points for which the second derivative of energy is positive for each and every coordinate. The second derivative gives the curvature of the coordinate at the point on the surface. A positive value for the second derivative indicates that the surface is curved down and corresponds to a maximum. Points for which the second derivative is positive for all dimensions correspond to "stable" molecules, although not necessarily molecules that can actually be isolated. The *second* are points for which the second derivative of the energy is positive for all coordinates except for one (the reaction coordinate) for which the second derivative of the energy is negative. These *may* correspond to transition states.

MOLECULAR MODELING: Geometries of Transition States and the Hammond Postulate, con't.

Even though they cannot be determined experimentally, the geometries of transition states are often brought up in the discussion of chemical reactions. For example, the choice of which regio or stereochemical product is preferred often comes down to which results from the "least crowded" transition state. Several examples of this appear in the succeeding problems in this chapter.

Another relationship that is commonly made is that between the geometry of the transition state and that of the reactants. According to the *Hammond Postulate*, the more *exothermic* a reaction the more its transition state will resemble the reactants. Said in reverse, the more the transition state resembles the reactants, the more *exothermic* a reaction is likely to be. The Hammond Postulate provides justification for use of the properties of reactants, for example, its steric demands, to anticipate the properties of the transition state.

Transition states obtained from quantum chemical calculations for Diels-Alder cycloadditions of cyclopentadiene and ethylene and for cyclopentadiene and tetracyanoethylene appear at the left and right of the screen, respectively. The first corresponds to a reaction that is very slow, that is, has a high energy barrier, while the second corresponds to a reaction that is very fast, that is, has a low energy barrier. According to the Hammond Postulate, which transition state should more closely resemble its reactants? Elaborate. Examine the two transition states to see if can find evidence supporting or refuting the suitability of the Hammond Postulate in this instance. You can calculate equilibrium geometries for the reactants (ethylene, tetracyanoethylene and cyclopentadiene) if you think that this will help.

MOLECULAR MODELING: Arrhenius Equation

While the geometries of transition states obtained from quantum calculations are certainly "interesting", in that they show the "making" and "breaking" of bonds on the way from reactants to products. Will they tell the chemist what really matters: "will a reaction go" and if it does "what products will be formed"? Put another way, do changes in structure fortell changes in activation energies and if they do, will they be large enough to discern?

Compare transition states for the Diels-Alder reaction of 2-methoxybutadiene and styrene leading to the *para* regioisomer (top left) and for the corresponding reaction of 2-methoxybutadiene and 2-butyne (top right). Can you see any difference in their geometries that would tell you that the first reaction is fast while the second reaction is slow? Specifically, is one of the transition states "more delocalized" and presumably more stable than the other transition state? A measure of this might be that the difference between formal, single, and double bonds (in the reactants) is more "blurred" in one of the transition states than in the other.



Next, compare transition states for Diels-Alder reactions involving 2-methylbutadiene as the diene, first with maleic anhydride (bottom left) and then with 2-cyclopenten-1-one leading to the *para*

MOLECULAR MODELING: Arrhenius Equation, con't.

regioisomer (bottom right) as dienophiles. Here, reaction with maleic anhydride is known to be much faster than that with 2-cyclopenten-1-one. Is one of the transition states more delocalized than the other (use the same criterion as before)? For these examples, do you find it easy or difficult to tell from examining the transition states, that one reaction is likely to be much faster than the other?

Questions about whether a particular reaction will actually occur and if it does, what its product will be may be answered by connecting the rates of chemical reactions to the energies of their transition states. This requires a model, the most common of which is known as the *Arrhenius equation*. According to the Arrhenius equation, the rate of a chemical reaction depends on the concentration of reactants, [R], the so-called pre-exponential or "A factor", which accounts for the fact that not all encounters between reactants will lead to reaction, and the energy barrier or *activation energy*, ΔE^{\ddagger} , that the reactants must surmount to get over the transition state. The activation energy is simply the difference the energy of the transition state and that of the reactants.

rate \propto [R] A exp[- $\Delta E^{\ddagger}/RT$]

R is the gas constant and T is the temperature (in K). Where the concern is which product is favored for a particular reaction, that is, where the reactants are the same, the experimental conditions (correlations) will be identical and the A factor may safely be assumed to be the same for all competing reactions. In this case, the dominant product will be that formed from the transition state with the lowest energy. So the goal is to identify the lowest-energy transition state among all possible transition states and link it to a product.

Back to the two examples referred to earlier in this problem. Based on an analysis of the activation energy, the results are clear. Diels-Alder reaction of 2-methoxybutadiene and styrene occurs with an activation energy that is 32 kJ/mol lower than that for reaction of 2-methoxybutadiene and 2-butyne, and the Diels-Alder reaction of 2-methylbutadiene and maleic anhydride occurs with an activation energy that is 44 kJ/mol lower than that for reaction of 2-methylbutadiene and 2-cyclopenten-1-one. These activation energy differences are large enough that competition between dienophiles styrene and 2-butyne in the case of 2-methoxybutadiene as a diene and maleic anhydride and 2-cyclopenten-1-one in the case of 2-methyl butadiene as a diene would not be close.

In summary, while comparison of the geometries of transition states for related reactions may not always lead to a clear assignment of relative reaction rates, comparison of activation energies will likely provide an reliable indicator.

MOLECULAR MODELING: Charge Transfer in Diels-Alder Reactions

Most synthetically-important Diels-Alder reactions involve electron-rich dienes and electrondeficient dienophiles. According to the picture first introduced by Woodward and Hoffmann, favorable interaction between the highest-occupied molecular orbital (the HOMO) on the diene and the lowest-unoccupied molecular orbital (the LUMO) on the dienophile stabilizes the transition state and lowers the activation energy. As a consequence, electrons should be transferred from filled to empty molecular orbitals, and be reflected in the charge distribution of transition state. In the case of the Diels-Alder reactions between electron-rich dienes and electron-deficient dienophiles,

MOLECULAR MODELING: Charge Transfer in Diels-Alder Reactions, con't.

electrons should move from the HOMO (on the diene) into the LUMO (on the dienophile). Does significant charge transfer actually occur? If it does, is the extent of transfer related to the degree to which the diene is electron rich and the dienophile is electron poor? Does greater charge transfer necessarily imply greater stabilization of the transition state and lower activation energy?

One measure of molecular charge distribution is provided by an electrostatic potential map. This colors each location on an electron density surface, indicating overall size and shape, with the value of the electrostatic potential, indicating the energy that a positive charge "feels" at this location. By convention, electron-rich regions where the charge is attracted are colored "red", whereas electron-poor regions where the charge is repelled are colored "blue". Compare electrostatic potential maps for the transition state for the Diels-Alder reaction of cyclopentadiene and acrolein (top right) with those of the reactants, cyclopentadiene (top left) and acrolein (top center). The maps are displayed as transparent models to allow you to see the underlying structures. Once you are properly oriented, switch to solid models to allow the extent of any differences to be ascertained. *Click* on one of the maps and select *Solid* from the **Style** menu at the bottom of the screen. Is there evidence of charge transfer between the reactants and their fragments in the transition state? Elaborate. If there is, is it in the direction supposed by the Woodward-Hoffmann model, that is, has the diene become "less red" and the dienophile "less blue"?

Next compare electrostatic potential maps for the transition state for the Diels-Alder reaction of cyclopentadiene and tetracyanoethylene (bottom right) with those of the reactants, cyclopentadiene (top left) and tetracyanoethylene (bottom center). This reaction is known to be faster (lower activation energy) than that involving acrylonitrile as a dienophile. Is the direction of charge transfer the same as that for the reaction involving acrylonitrile? If it is, is the magnitude of the transfer, smaller, larger or about the same? Does there appear to be a link between the extent of charge transfer and rate for Diels-Alder reactions? Elaborate.

11.4.C. Selectivity in the Diels-Alder Reaction

The Diels-Alder reaction is one of the powerful reactions, as categorized by Corey in the LHASA program (sec. 10.4.B). One of the powerful features of the Diels-Alder reaction is the stereochemical selectivity inherent to the cycloaddition, and many examples exist in the total synthesis of natural products.⁸⁰

11.4.C.i. Cis-Trans Selectivity. In the reaction of **32**, the cycloadduct (**33**) showed a cis relationship at the ring juncture. The methyl and the hydrogen at the bridgeheads were derived from the respective alkene and it is clear that the relative stereochemistry of these groups in the alkene reactant was retained in the Diels-Alder cycloadduct (**33**). As seen in the transition state for that reaction, as butadiene approached the alkene, the hydrogen and the methyl were

 ⁽a) Nicolaou, K.C.; Snyder, S.A.; Montagnon, T.; Vassilikogiannakis, G. Angew. Chem. Int. Ed., 2002, 41, 1669; (b) Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G.P. Natural Product Synthesis Through Pericyclic Reactions, American Chemical Society, Washington, 1983, pp 119-254.

pushed away, and no isomerization occurred during the reaction. The product (33) reflected this stereochemistry, with the methyl and hydrogen cis to each other. In general, reactions requiring relatively low reaction temperatures and fast reaction times show little epimerization (*cis* \rightarrow *trans*). Maleic anhydride reacted with butadiene in refluxing xylene to give the cis cycloadduct (40), which was opened under the reaction conditions to the cis-diacid (41).⁸¹ The cis configuration of the alkene reaction partner (maleic anhydride) is locked by the cyclic nature of the anhydride, and retained in the product. When the stereochemistry is not locked, it can be controlled in some cases. When 1-phenyl-1,3-butadiene reacted with acryloyl chloride, for example, the cis adduct (42) was formed, but at refluxing temperatures, a mixture of 42 and 43 was formed, with 43 predominating.⁸² This example illustrates that epimerization to a more stable product is possible when the product contains an α -hydrogen that is subject to enolization.



In the monograph by Desimoni et al.,⁸³ four rules are listed for Diels-Alder reactions, taken from Sauer's work⁸⁴ and based on molecular orbital arguments.

- 1. Electron-withdrawing substituents (Z) on dienophiles and electron releasing substituents (X) on dienes increase the rate of reaction. The reverse substituent effects (inverse electron demand) likewise increase the rate.
- 2. The diene and dienophile configurations are retained in the adduct (the cis principle).
- 3. The endo transition state is favored over the exo transition state (the endo rule).
- **4.** The Z-substituted dienophiles react with 1-substituted butadienes (in normal electron demand Diels-Alder reactions) to give 3,4-disubstituted cyclohexenes, independent of the nature of diene substituents (the **ortho effect**).

The effects of electron-withdrawing and releasing substituents on a diene (Rule 1) were previously discussed, and the stereochemistry of the alkene (dienophile, Rule 2) was retained

^{81.} Korolev, A.; Mur, V. Dokl. Akad. Nauk. SSSR 1948, 59, 251.

^{82.} Meek, J.S.; Poon, B.T.; Merrow, R.T.; Christol, S.J. J. Am. Chem. Soc. 1952, 74, 2669.

^{83.} Reference 80b, pp 128-130.

^{84.} Sauer, J. Angew. Chem. Int. Ed. 1966, 5, 211; (b) Idem Ibid. 1967, 6, 16.

in the cycloadduct. An illustration is the reaction of *E*,*E*-diene **44** with maleic anhydride to give **45**.^{85,86} Similarly, *E*,*Z*-butadienes **46** reacted with maleic anhydride to give cycloadduct **47**.^{87,88} With a wide range of substrates, the stereochemistry of the substituents in the diene was retained in the cycloadduct.



In order for the stereochemistry of the diene substituents to be maintained in 45 and 47, the relative motions of these substituents during ring formation must be as shown in 50. The outer substituents on the diene move toward each other, and the inner substituents move away from each other producing 51. Such motion is described as **conrotatory** (orbital motion in the same direction; $50 \rightarrow 51$). Alternatively, the outer substituents can move in opposite directions, as indicated in 48, and is termed **disrotatory** (orbital motion in opposite directions, $48 \rightarrow 49$).⁸⁹ It is clear from previous examples that the Diels-Alder reaction proceeded with a disrotatory motion in those cases, leading to predictable stereochemistry in the cycloaddition. The Merck cortisone synthesis, performed by Sarett et al.⁹⁰ began with reaction of **52** and benzoquinone to give **53**. The cis stereochemistry at the ring juncture is predictable by examination of transition state shown. Disrotatory motion of the methyl and hydrogen led to the stereochemistry shown in **53**.



- 86. Alder, K.; Schumacher, M. Annalen 1951, 571, 87.
- 87. Reference 86, pp 544-545.
- 88. Alder, K.; Vogt, W. Annalen 1951, 571, 137.
- 89. Also see David, C.W. J. Chem. Ed. 1999, 76, 999.
- (a) Sarett, L.H.; Arth, G.E.; Lukes, R.M.; Beyler, R.E.; Poos, G.I.; Johns, W.F.; Constantin, J.M. J. Am. Chem. Soc. 1952, 74, 4974; (b) Sarett, L.H.; Lukes, R.M.; Poos, G.I.; Robinson, J.M.; Beyler, R.E.; Vandergrift, J.M.; Arth, G.E. Ibid. 1952, 74, 1393.

^{85.} Martin, J.G.; Hill, R.K. Chem. Rev. 1961, 61, 537 (see p 544).



MOLECULAR MODELING: Conformation and the Rates of Diels-Alder Reactions

Calculations indicate that the activation energy for the Diels-Alder reaction of cyclopentadiene and acrylonitrile is 29 kJ/mol less than that for the corresponding reaction of (*trans*) 1,3-butadiene and acrylonitrile. One possible explanation is that the lowest-energy conformer of 1,3-butadiene is s-*trans* and not s-*cis*. Thus, energy needs to be expended to get into the "reactive" s-*cis* conformer. An alternative explanation is that the π system of cyclopentadiene may be inherently more electron rich than that of 1,3-butadiene, that is, cyclopentadiene is a better diene.

Obtain energies for both s-*cis* and s-*trans* conformers of 1,3-butadiene. Note that the *cis* diene may not be planar, so start with a non-planar structure. You can rotate around the carbon-carbon single bond by *clicking* on it, holding down both the left mouse button and the **Alt** key (**Option** key on Macintosh) and moving the mouse up and down. What is the energy difference between the "reactive" *cis* conformer of 1,3-butadiene and the *trans* conformer? Is conformation a possible explanation for the difference in reactivity of the two dienes? Compare electrostatic potential maps for *cis*-1,3-butadiene and cyclopentadiene. Which diene appears to be more electron rich? Is this difference a possible explanation for the difference in reactivity of the two dienes?

Next, try to explain why the Diels-Alder reaction of 2,3-dimethylcyclopentadiene and acrylonitrile is faster that that between 2,3-dimethyl-1,3-butadiene and acrylonitrile. Identify the lower-energy conformer for 2,3-dimethyl-1,3-butadiene. If it is not the "reactive" (s-*cis*) conformer, what is the energy that must be expended before the Diels-Alder reaction can take place? Is the "penalty" smaller, larger or about the same as for 1,3-butadiene? Given that the activation energy for the reaction of 2,3-dimethyl-1,3-butadiene and acrylonitrile is 29 kJ/mol lower than that for corresponding reaction of 2,3-dimethylcyclopentadiene, what if anything does your result suggest about the importance of conformation on relative rate. Compare electron rich? What if anything does your result suggest about the importance of the "electron richness" of the diene on relative rate?

11.4.C.ii. Regioselectivity of Cycloaddition Reactions. It is apparent from several of the preceding examples that more than one regioisomeric cycloadduct is possible with certain

substituent patterns on the diene and/or alkene. When the 2-substituted diene **54** reacts with alkene CH_2 =CHX, two orientations for the X group are possible relative to R: the meta orientation in **55** and the para orientation in **56**. Dienes with substituents at C1, such as **57**, react with CH_2 =CHX to give a mixture of the ortho product (**58**) and the meta product (**59**). Although a mixture of regioisomers is formed, the Diels-Alder reaction is highly regioselective in most cases. The reaction of 1,3-pentadiene and methyl acrylate, for example, gave a 68% yield of the ortho adduct, **60**.⁹¹ Similarly, 1-phenyl-1,3-butadiene reacted with acrolein to give **61**, in 64% yield.⁷⁴ The endo products are cis **60** and **61**. In the Diels-Alder reaction of 1-alkyl butadienes (**57**, R = Me, *i*-Pr, *n*-Bu, *t*-Bu) with CH₂=CHX (X = CHO, CN, CO₂Me), the ortho regioisomer **58** was favored over the meta cycloadduct (**59**),⁹² with a preference between 4:1 and 10:1.



The propensity for ortho, meta, or para selectivity will vary with the diene (electron-releasing or withdrawing substituents) and the alkene (electron-releasing or withdrawing substituents). Fleming assembled a table to predict regioselectivity for the generalized alkenes CH_2 =CH–R, CH_2 =CH–Z, and CH_2 =CH–X (where R = an alkyl group, Z = an electron-withdrawing group, and X = an electron-releasing group) using frontier orbital considerations.⁹³

Examining the orbital coefficients of the HOMO and LUMO for both diene and alkene predicts selectivity. The transition state for the reaction of methyl acrylate and 2-phenyl-1,3-butadiene (see **62**) shows the orbitals with largest coefficients (HOMO_{diene}-LUMO_{alkene}) combine (the absolute value of the orbital coefficient is used, $|-0.625| \leftrightarrow |0.69|$ and $|-0.475| \leftrightarrow |-0.471|$) to predict the cycloadduct produced in the greatest amount (the para product, **63**). The HOMO₆₂-LUMO_{alkene} ΔE is [0 - (-8.77) = 8.77], and it predicts the relative reactivity of these reactants. The magnitude of the orbital coefficients in each partner is important, and overlap of the larger orbital coefficients are 0.625 for the diene and 0.69 for the alkene, and their overlap predicts the observed selectivity for the para product. Similarly, the orbital coefficients for 1-methoxy-

^{91.} Meek, J.S.; Ragsdale, J.W. J. Am. Chem. Soc. 1948, 70, 2502.

^{92. (}a) Reference 80b, p 137; (b) Titov, Y.A. Usp. Khim. 1962, 31, 529.

^{93.} Reference 7, pp 133-138.

1,3-butadiene and acrolein correctly predict the major product is the ortho adduct. For simple cases, the orbital coefficients can be calculated, using a program such as Spartan^M.⁴⁰



This discussion allows an explanation of the **ortho effect** presented earlier, in connection with the Diels-Alder reaction. When a C=X or a C=X unit (where X is a heteroatom) reacts with a 1-substituted diene, the ortho product is generally preferred. Ortho selectivity is explained by the size of the orbital coefficients. When coefficient size is combined with secondary orbital interactions (sec. 11.4.C),^{47,43,94} as indicated in the transition state shown in Figure 11.10, the carbonyl orbital is responsible for a secondary interaction that stabilizes the ortho transition state. If the meta transition state is involved, then orbital symmetry dictates an exo mode, and there is no possibility for secondary orbital interactions. Secondary orbital interactions such as this are possible only in an endo transition state. The application of secondary orbital interactions to this problem has been questioned.⁹⁵



Figure 11.10. Frontier Orbital Control of Regiochemistry For Electron-Rich Dienes and Acrolein.

The ability to predict the regioselectivity of Diels-Alder reactions is a cornerstone of their use in synthesis. Methyl vinyl ketone (MVK), for example, reacted with 2-methyl-1,3-butadiene to give a 3:1 mixture of **64** and **65**. Gutsche et al. used the para product (**64**) to synthesize α -bisabalol.⁹⁶ They also reported that using stannic chloride as a catalyst (to be discussed in sec. 11.6.A) increased the ratio of **64/65** to 93:7.⁹⁶

^{94.} Also see Eisenstein, O.; Lefour, J.-M.; Ahn, N.T. Chem. Commun. 1971, 969.

^{95.} Fleming, I.; Michael, J.P.; Overman, L.E.; Taylor, G.F. Tetrahedron Lett. 1978, 1313.

^{96. (}a) Gutsche, G.D.; Maycock, J.R.; Chang, C.T. *Tetrahedron* 1968, 24, 859; (b) Rittersdorf, W.; Cramer, F. *Ibid.* 1968, 24, 43.



The diene and/or the alkene components can be part of a amore complex structure. An example is the reaction of the C=C unit in conjugated lactam **66** with the conjugated diene-yne **67**, taken from a synthesis of (–)-gymnodimine by Romo and co-workers.⁹⁷ A chiral *bis*-oxazolone **68**-hexafluoroantimonate complex catalyzes the reaction⁹⁸ to give **69** in 85% yield, and 95% ee.



Hehre et al. proposed an alternative method to predict the regioselectivity of Diels-Alder reactions. The FMO approach does not predict "that a phenyl substituent is a significantly better regiodirector than methyl".^{14,99} Hehre suggested using the average hydride potentials for the carbons of substituted ethylenes,¹⁴ and the electrostatic (proton) potentials for the carbons of substituted dienes.¹⁴ Correlating the largest coefficients of each reactive pair of molecules can accurately predict the regioselectivity of the resulting cycloadduct.

11.4.C.iii. Endo Selectivity. In the reaction that generated **53**, the observed stereochemistry demanded that the benzoquinone be under the diene at the time of reaction (see that transition state in sec. 11.4.C.i), which is the normal reaction of dienophiles bearing a substituent with a π -bond and is called an **endo mode** of addition (the group of interest is under or down, relative to the diene, rather than out or up). This endo addition is seen again in the reaction of diene **70** with methacrolein to give **71**, via the endo transition state shown, taken from Rawal and Kozmin's synthesis of (–)- α -elemene.¹⁰⁰ In this case, the disrotatory motion of the pyrrolidine unit places it down in the transition state. The carbonyl moiety is endo in the transition state, leading to the observed cis geometry (CHO and pyrrolidino in **71**). This endo orientation is seen again in the transition state for a reaction of acrylic acid with a generic diene (**72**) and

^{97.} Kong, K.; Moussa, Z.; Romo, D. Org. Lett. 2005, 7, 5127.

^{98. (}a) Evans, D.A.; Miller, S.J.; Lectka, T.; Matt, P.V. J. Am. Chem. Soc. 1999, 121, 7559. (b) Evans, D.A.; Barnes, D.M.; Johnson, J.S.; Lectka, T.; von Matt, P.; Miller, S.J.; Murry, J.A.; Norcross, R.D.; Shaughnessy, E.A.; Campos, K R. J. Am. Chem. Soc. 1999, 121, 7582.

^{99.} Also see Hehre, W.J.; Pau, C.F.; Hout Jr., R.F.; Francl, M.M. Molecular Modeling - Computer Aided Descriptions of Molecular Structure and Reactivity, Wiley, New York, **1987**.

^{100.} Kozmin, S.A.; Rawal, V.H. J. Am. Chem. Soc. 1997, 119, 7165.

it contrasts with the exo orientation in 74, which gives the opposite relative stereochemistry for the ring substituents (trans- in 75 vs. cis- in 73). In many reports of Diels-Alder reactions spanning many years the endo orientation is preferred, usually in a ratio of $2\rightarrow$ 4:1, which is the basis of rule 3 listed previously, the so-called **endo rule** or **Alder endo rule**.¹⁰¹ Martin and Hill define the rule as follows: "Endo addition involves the tendency for dienophile substituents to be so oriented in the favored transition state that they lie directly above the residual unsaturation of the diene.... The transition state that is best stabilized by spatial orbital overlap and simultaneously least destabilized by unfavorable steric repulsion has the lowest free energy of all possible transition states, and consequently predominates in the kinetically determined product".⁸⁵



An endo transition state is best observed in reactions with cyclic dienes such as cyclopentadiene, where the exo/endo orientation is easily detected in the cycloadduct. Cyclopentadiene, for



example, reacts to give an endo product (X group is under the ring in **76**) and an exo product (X group is up as in **77**).¹⁰² Both electron-rich and -poor substituents (X) on the alkene exhibit endo selectivity upon reaction with cyclopentadiene

^{101.} Alder, K.; Stein, G. Angew. Chem. 1937, 50, 510.

^{102.} Reference 85, p 546.



The Alder endo rule is explained by FMO theory, invoking secondary orbital interactions.¹⁰³ A comparison of the endo transition state (78) with the exo transition state (79) for the reaction of cyclopentadiene and acrolein shows the orbitals of the carbonyl are properly aligned in 78 and of the correct symmetry for stabilization by the orbitals of

the HOMO_{diene}. This interaction is absent in the exo transition state (**79**). This secondary orbital interaction stabilizes **78** and lowers the energy of that transition state relative to **79**. Maleic anhydride¹⁰⁴ reacts with cyclopentadiene, for example, to give only the endo product, and in like manner *cis*-methacrylic acid reacts to give a 90:10 mixture of endo/exo cycloadducts.¹⁰⁵ As mentioned in section 11.4.C.ii for the ortho effect, the existence of secondary orbital interactions for explaining endo selectivity has been called into question.¹⁰⁶ Indeed, Ogawa and Fujimoto¹⁰⁷ demonstrated by the application of perturbation theory that the effect of secondary orbital interactions should be much less significant than has been assumed within the frontier orbital scheme. Somekawa and co-workers reported calculations that concluded selectivity arises from interactions of the diene π and n orbitals, as well as the diene- π orbitals and dienophile- π orbitals.¹⁰⁸

Examination of such interactions is important for the understanding of regioselectivity in Diels-Alder reactions. Houk formulated a general approach for secondary orbital interactions.¹⁰⁹

- 1. For all allowed cycloadditions involving the reaction of a 4n electron polyene with an alkene with extended conjugation, the endo transition state can be stabilized by secondary orbital interaction (see 80 and 81).
- 2. For the allowed 4n + 4m+2 cycloaddition of two polyenes, where $m \neq 0$, the endo transition state will be destabilized (see 82).¹¹⁰

106. García, J.I.; Mayoral, J.A.; Salvatella, L. Acc. Chem. Res. 2000, 33, 658.

- 108. Kiri, S.; Odo, Y.; Omar, H.I.; Shimo, T.; Somekawa, K. Bull. Chem. Soc. Jpn. 2004, 77, 1499.
- 109. Houk, K.N. Tetrahedron Lett. 1970, 2621.

^{103.} Hoffmann, R.; Woodward, R.B. J. Am. Chem. Soc. 1965, 87, 4388, 4389.

^{104.} Alder, K.; Stein, G.; von Buddenbrock, F.; Eckardt, W.; Frercks, W.; Schneider, S. Annalen 1934, 514, 1.

^{105.} Alder, K.; Günzl, W.; Wolff, K. Chem. Ber. 1960, 93, 809.

^{107.} Ogawa, A.; Fujimoto, H. Tetrahedron Lett. 2002, 43, 2055.

^{110.} Reference 2, pp 228-229.



11.5. INVERSE ELECTRON DEMAND AND THE RETRO DIELS-ALDER

Two variations for the Diels-Alder reaction are synthetically useful. In one, the HOMO-LUMO interactions that drive the reaction change due to heteroatoms and/or substituents on the diene and/or alkene units. The reaction is driven by the LUMO_{diene}-HOMO_{alkene} interaction rather than the HOMO_{diene}-LUMO_{alkene} interaction. The second uses the reversible nature of the Diels-Alder reaction. Manipulation of the cycloadducts followed by a retro-Diels-Alder reaction gives a new diene or alkene. Both variations will be examined in this section.

11.5.A. Inverse Electron Demand Diels-Alder Reactions

The LUMO_{diene}-HOMO_{alkene} interaction for butadiene and methyl vinyl ether is lower than the comparable HOMO_{diene}-LUMO_{alkene} interaction in dienes bearing an electron-withdrawing group. In some cases this leads to the **inverse electron demand** reaction mentioned above. Fleming uses the example of azonia salt **83**,¹¹¹ which reacted with diethyl ketene acetal to give **84**. Similar reaction with allyl alcohol gave **85**, and acrylonitrile gave **86**.^{111a} In all examples, the reaction proceeded to 75% completion and the relative rates of reactions provided with each transformation indicates that electron-rich alkenes reacted faster. Inverse electron demand Diels-Alder reactions are controlled by the LUMO_{diene} HOMO_{alkene} interaction, which usually means that an electron-rich alkene reacts faster than an electron-poor alkene, the opposite of what is normally observed (see above).

 ⁽a) Reference 7, pp 111-112; (b) Fields, D.L.; Regan, T.H.; Dignan, J.C. J. Org. Chem. 1968, 33, 390; (c) Porter, N.A.; Westerman, I.J.; Wallis, T.G.; Bradsher, C.K. J. Am. Chem. Soc. 1974, 96, 5104.



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In another example, Boger and Kasper prepared 1-azadiene **87** (azadienes are discussed in sec. 11.7.C.v) and showed that the LUMO of the diene controlled the subsequent Diels-Alder reaction. Reaction of **87** with butyl vinyl ether

(*n*-BuOCH=CH₂) gave a 74% yield of 88 (>20:1 endo/exo).¹¹² This reaction was sluggish and high pressure (sec. 11.6.C) was required to force the reaction to product with a reasonable reaction time and in good yield. Boger and co-workers also showed that tetrazines react with alkynes, with inverse electron demand, to give 1,2-diazines, after loss of nitrogen from the original Diels-Alder cycloadduct.¹¹³ It is apparent from these few examples that the structures of most reverse electron demand Diels-Alder reactions involve heteroatoms, or another unique feature. They are less prevalent than the normal electron demand Diels-Alder reactions discussed elsewhere in this chapter. A synthetic example is taken from Dang and co-worker's synthesis of purine nucleosides¹¹⁴ for which 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine (91), a useful diene used by Boger for the synthesis of pyrimidines,¹¹⁵ reacted with 5-amino-1-benzyl-4-imidazolecarboxylic acid (89) to give 94 in 83% yield. Decarboxvlation of 89 occurred during the reaction to give the reactive species 90 prior to the Diels-Alder reaction, which gave cycloadduct 92.114 This compound was not isolated, but rather decarboxylated to give 93, and this compound lost ammonia to give the observed product. Imidazole 90 is so reactive, that this reaction occurs at the relatively mild conditions shown, which is somewhat unusual for inverse-electron demand Diels-Alder reactions.

^{112.} Boger, D.L.; Kasper, A.M. J. Am. Chem. Soc. 1989, 111, 1517.

^{113.} Soenen, D.R.; Zimpleman, J.M.; Boger, D.L. J. Org. Chem. 2003, 68, 3593.

^{114.} Dang, Q.; Liu, Y.; Erion, M.D. J. Am. Chem. Soc. 1999, 121, 5833.

See (a) Boger, D.L.; Dang, Q. J. Org. Chem. 1992, 57, 1631; (b) Boger, D.L.; Menezes, R.F.; Dang, Q. J. Org. Chem. 1992, 57, 4333; (c) Boger, D.L.; Kochanny, M.J. J. Org. Chem. 1994, 59, 4950.



Enantioselective inverse-electron demand hetero-Diels-Alder reactions have been reported. Jorgensen and Juhl reported that 3-methybutanal reacted with conjugated ketone **95** in the presence of a catalytic amount of a chiral pyrrolidine to give the Diels-Alder adduct thast led to **96** in 93% overall yield, and 89% ee after oxidation with PCC.¹¹⁶ This catalytic procedure is believed to proceed by initial formation of the pyrrolidine enamine of the aldehyde, followed by an inverse electron demand Diels-Alder reaction. In the presence of water and silica, the *N*,*O*-acetal is converted to the hemi-acetal, which is then oxidized with PCC. Jacobsen and co-workers reported that chromium complex **97** showed catalyzed the inverse electron Diels-Alder reaction of ten equivalents of ethyl vinyl ether and 2-butenal, to give pyran **98**, in 75% yield and 94% ee.¹¹⁷



^{116.} Juhl, K.; Jørgensen, K.A. Angew. Chem. Int. Ed., 2003, 42, 1498.

^{117.} Gademann, K.; Chavez, D.E.; Jacobsen, E.N. Angew. Chem. Int. Ed. 2002, 41, 3059.

A typical inverse electron demand disconnection is:



11.5.B. Retro Diels-Alder Reaction

The Diels-Alder reaction is reversible under certain circumstances.¹¹⁸ This reversibility can be exploited synthetically with the correct choice of diene, dienophile and reaction conditions because the equilibrium usually favors the thermodynamically more stable cycloadduct as the major product. Woodward and Baer showed that maleic anhydride reacted with fulvalene **99** at ambient temperatures to give **100** the endo product (see below).¹¹⁹ When heated to 50°C for 10 min., however, **101** was the major product with only 20.5% of **100**, and this dropped to 3.1% upon heating at 50°C for 60 min.¹¹⁹ This result is consistent with a reversible reaction pathway favoring the more stable exo product.¹¹⁹ This reverse reaction (cycloadduct \rightarrow diene + dienophile) is called a **retro Diels-Alder reaction**.¹²⁰



A classical example of a retro Diels-Alder reaction is the self condensation of cyclopentadiene (20) to give the cyclopentadienyl dimer 102. This reaction occurs quickly at temperatures



> 25°C, but is slow at low temperatures such as
 H -78°C. Many Diels-Alder reactions involving cyclopentadiene are done at low temperatures with Lewis acid catalysts (sec. 11.6.A) to suppress

cyclopentadiene dimerization. When heated to 160-240°C, a retro-Diels-Alder reaction of **102** gives 2 equivalents of monomeric cyclopentadiene.¹²¹

 ⁽a) Kwart, H.; King, K. Chem. Rev. 1968, 68, 415; (b) Smith, G.G.; Kelly, F.W. Progr. Phys. Org. Chem. 1971, 8, 75 (see p 201).

^{119.} Woodward, R.B.; Baer, H. J. Am. Chem. Soc. 1944, 66, 645.

^{120. (}a) Ripoll, J.L.; Rouessac, A.; Rouessac, F. *Tetrahedron* 1978, 34, 19; (b) Lasne, M.-C.; Ripoll, J.L. *Synthesis* 1985, 121; (c) Ichihara, A. *Ibid.* 1987, 207.

 ⁽a) Moffett, R.B. Org. Synth. Coll. Vol. 4 1963, 238; (b) Korach, M.; Nielsen, D.R.; Rideout, W.H. Org. Synth. Coll. Vol. 5 1973, 414.

Most of the synthetic applications of retro-Diels-Alder reactions involve cyclopentadiene or furan diene partners, but alkyne dienophiles are common and there are many potential substrate. One example is illustrated in Baran and Burns' synthesis of haouamine A in which a dilute solution of pyrone **103** was heated in *o*-dichlorobenzene with BHT to give cycloadduct **104**, which lost CO₂ via a retro-Diels-Alder reaction to give a 21% yield of **104** (+ 30% of **103**) after hydrolysis of the acetoxy groups.¹²² The retro-Diels-Alder usually requires higher temperatures than the Diels-Alder reaction, and the normal Diels-Alder reaction is desired, flash vacuum pyrolysis is a common technique used in synthesis.¹²³ Lewis acids also catalyze retro-Diels-Alder reactions (sec. 11.6.A).¹²⁴ In a synthesis of pentenocin B, Sugahara, Fukuda and Iwabuchi utilized a retro Diels-Alder reaction beginning with ketodicyclopentadiene **106**.¹²⁵ Compound **106** was converted in ten steps to the highly functionalized compound **107**. When **107** was heated to 280°C, the retro-Diels-Alder reaction liberated cyclopentadiene and the targeted conjugated ketone **108** in 93% yield.



A variety of interesting and useful products are available by using the Diels-Alder reaction to insert functionality and the retro-Diels-Alder to transform that product into another. The retro-Diels-Alder reaction therefore leads to several interesting disconnections, including

^{122.} Baran, P.S.; Burns, N.Z. J. Am. Chem. Soc. 2006, 128, 3908.

^{123.} Stork, G.; Nelson, G.L.; Rouessac, F.; Gringore, O. J. Am. Chem. Soc. 1971, 93, 3091.

^{124.} Grieco, P.A.; Abood, N. J. Org. Chem. 1989, 54, 6008.

^{125.} Sugahara, T.; Fukuda, H.; Iwabuchi, Y. J. Org. Chem. 2004, 69, 1744.



11.6. RATE ENHANCEMENT IN DIELS-ALDER REACTIONS

In many instances, Diels-Alder reactions give poor yields and/or require excessively harsh reaction conditions and long reaction times. There are several fairly straightforward techniques that increase the rate and, in some cases, the selectivity of Diels-Alder reactions. The three most important methods are catalysis by Lewis acids, rate enhancement in aqueous media, and the use of high pressure (usually greater than 5 kbar). The exploration of the Diels-Alder reaction in environmentally friendly solvents such as ionic liquids is also of great interest. Two common ionic liquids are [bmim] [BF₄] or [bmim][ClO₄], and [emim][PF₆], where [bmim]⁺ and [emim]⁺ are 1-butyl-3-methylimidazolium (**109**) and 1-ethyl-3-methylimidazolium (**110**), respectively.¹²⁶ Both hydrogenbutylimidazolium tetrafluoroborate (HBuIm, **111**) and 1,3-dibutylimidazolium, tetrafluoroborate (DiBuIm, **112**)¹²⁷ have been used in Diels-Alder reactions,¹²⁸ where these compounds were the ionic liquid medium. An asymmetric Diels-Alder reaction was reported using ionic liquids.¹²⁹ Pyridinium based ionic liquids such as ethylpyridinium tetrafluoroborate (**113**) have also been used.¹³⁰ The use of green solvents such as these is an important, and rapidly expanding area of research.



^{126.} Kumar, A. Chem. Rev. 2001, 101, 1 (see p. 8).

^{127.} For discussion of HBuIM and DiBuIm, see (a) Harlow, K. J.; Hill, A. F.; Welton, T. Synthesis 1996, 697;
(b) Holbrey, J. D.; Seddon, K. R. J. Chem. Soc. Dalton Trans. 1999, 2133; (c) Larsen, A. S.; Holbrey, J. D.; Tham, F. S.; Reed, C. A. J. Am. Chem. Soc., 2000, 122, 7264.

^{128.} Jaegar, D. A.; Tucker, C. E. Tetrahedron Lett. 1989, 30, 1785.

^{129.} Meracz, I.; Oh, T. Tetrahedron Lett. 2003, 44, 6465.

^{130.} See Xiao, Y.; Malhotra, S.V. Tetrahedron Lett. 2004, 45, 8339.

11.6.A. Catalysis by Lewis Acids

Lewis acids are, in general, excellent catalysts for the Diels-Alder reaction.¹³¹ Their catalytic activity lies in the ability of the Lewis acid to complex a heteroatom component of the diene or dienophile (usually the dienophile). Complexation with acrolein, for example, generates an

ionic intermediate such as **114**,¹³² and this zwitterion will influence the course of the Diels-Alder reaction.¹³³ Formation of **114** lowers the net energy of both the HOMO and the LUMO relative to the uncomplexed



dienophile.¹³⁴ Protonated acrolein was used to mimic **114**, and the energy lowering of these frontier molecular orbitals was significant.¹³⁴ Ottenbrite and co-workers calculated the HOMO/LUMO energies, as well as the orbital coefficients, for acrolein and the boron trifluoride complex, as shown in Figure 11.11.¹³⁵ In the reaction of acrolein with a suitable diene, ΔE for the HOMO_{diene}-LUMO_{alkene} will be lowered when comparing the acrolein reaction with the protonated acrolein reaction. The HOMO/LUMO energies and orbital coefficients were calculated¹³⁴ and are different from those presented in Table 1.1. Using the LUMO values of 3.68 eV and 1.05 eV reported by Ottenbrite,¹³⁵ the ΔE (HOMO_{diene}-LUMO_{alkene}) for reaction with cyclopentadiene is lowered from 12.65 for acrolein to 10.02 eV for the BF₃ complex in a reaction with cyclopentadiene (HOMO = -8.97 eV from Table 1). The lower ΔE predicts acceleration of the Diels-Alder reaction upon addition of the Lewis acid. An alternative view of this effect sees that the denominator in Equation (11.1) is lowered, which lowers the activation of the reaction when the Lewis acid lowers the HOMO and LUMO energies.



131. (a) Yates, P.; Eaton, P. J. Am. Chem. Soc. 1960, 82, 4436; (b) Fray, E.I.; Robinson, R. Ibid. 1961, 83, 249.

- 133. Thompson, H.W.; Melillo, D.G. J. Am. Chem. Soc. 1970, 92, 3218.
- 134. (a) Houk, K.N.; Strozier, R.W. J. Am. Chem. Soc. 1973, 95, 4094; (b) For a computational study of the BF₃catalyzed cycloaddition of furan and methyl vinyl ketone, see Avalos, M.; Babiano, R.; Bravo, J.L.; Cintas, P.; Jiménez, J.L.; Palacios, J.C.; Silva, M.A. J. Org. Chem. 2000, 65, 6613.
- 135. Guner, O.F.; Ottenbrite, R.M.; Shillady, D.D.; Alston, P.V. J. Org.. Chem. 1987, 52, 391.

^{132.} Reference 7, p 162.

The orbital coefficients are influenced by the extent of coordination with the Lewis acid.¹³² All orbital coefficients of acrolein (115) are affected (see the protonated form 116), but those of the alkene mojeties are changed less than those of the carbonyl, bringing about rather large effects in the HOMO and in the LUMO. The carbonyl carbon is most affected, as expected.^{132,136} In the reaction of acrolein with 2-phenylbutadiene, the para product (117) is preferred in the uncatalyzed reaction. The difference in orbital coefficients is much greater in the catalyzed reaction, and this leads to a greater preference for the para product in the catalyzed reaction, due to more efficient overlap of the larger coefficients. Therefore, a common benefit of Lewis acid catalysis is greater regioselectivity in the cycloadduct.¹³⁷ In general, the Lewis acid decreases the reaction time, and increases product yield and selectivity. Reaction with cyclopentadiene derivatives generally show increased endo selectivity when done in the presence of aluminum chloride.¹³⁸ Aluminum chloride increases the endo/exo ratio to favor the endo-product and the anti/syn ratio to favor the anti product. The syn/exo product was not formed in reportable amounts, presumably due to the severe steric interaction between the anti-chlorine and an exo-carbomethoxy. Stronger Lewis acids (AlCl₃ > TiCl₄ > BF₃, see sec. 2.3) have a greater effect on this reaction. Increased selectivity and rate of reaction are also observed with acyclic dienes. Additional examples of Lewis acid catalysis will be presented throughout this chapter. There is also a report that amidinium ions catalyze the Diels-Alder reaction.¹³⁹



MOLECULAR MODELING: Catalysis of Diels-Alder Reactions by Lewis Acids

The "important" orbital interaction for Diels-Alder cycloadditions involving electron-rich dienes and electron-poor dienophiles is that between the diene HOMO and the dienophile LUMO. Changes that diminish the separation of those orbitals (the *HOMO-LUMO gap*), either by raising the energy of the HOMO or lowering the energy of the LUMO (or both), will increase this interaction and should accelerate the reaction. One way to accomplish this is to add a Lewis acid such as BF₃ which complexes to the dienophile and lowers the energy of the LUMO. For example, quantum chemical calculations show a reduction in the activation energy for cycloaddition of cyclopentadiene and acrylonitrile of 43 kJ/mol as a result of complexing BF₃ end-on to the nitrogen in the dienophile. This suggests an increase in reaction rate, consistent with experimental observation.

A Lewis acid should also change the shape of the dienophile LUMO, leading to changes in regioselectivity of Diels-Alder reactions. For example, quantum chemical transition-state

^{136.} Reference 7, p 163.

^{137.} Williamson, K.L.; Hsu, Y.-F.L. J. Am. Chem. Soc. 1970, 92, 7385.

^{138.} Sauer, J.; Kredel, J. Tetrahedron Lett. 1966, 731.

^{139.} Schuster, T.; Kurz, M.; Göbel, M.W. J. Org. Chem. 2000, 65, 1697.

MOLECULAR MODELING: Catalysis of Diels-Alder Reactions by Lewis Acids, con't.

calculations show that the "uncatalyzed" reaction of 1-methylcyclopentadiene and acrylonitrile leads to a room-temperature ratio of *ortho* to *meta* products of 81:19, whereas the BF₃ catalyzed reaction increases the ratio to 99:1. Similarly, while the uncatalyzed reaction of 2-methylcyclopentadiene and acrylonitrile is non-regioselective (yielding a 55:45 ratio of *para* to *meta* products), but the BF₃ catalyzed reaction leads to a ratio of 70:30 (*para:meta*).

Examine and compare LUMO maps for acrylonitrile (left) and the acrylonitrile-BF₃ complex (right). These color a surface of electron density according to the value of the LUMO at a particular point on the surface. By convention, regions where the LUMO is most concentrated are colored "blue", while those where it is least concentrated are colored "red". The maps are displayed as transparent models allowing you to see the structure underneath. Once you are oriented, you can switch to solid models, by *clicking* anywhere on the map and selecting *Solid* from the Style menu at the bottom of the screen. For which carbon of acetonitrile is the LUMO more concentrated? Is the direction of the preference the same for the BF₃ complex? If it is, is the magnitude of the preference diminished or amplified, or does it not change significantly.

The HOMO in 1-methylcyclopentadiene is more concentrated on the unsubstituted double bond and the HOMO in 2-methylcyclopentadiene is more concentrated on the substituted double bond. Which regioisomer should be favored for each cycloaddition with the alkenes noted above? Assume that the preferred product will be that where the carbon on the diene with the higher HOMO concentration will position itself over the carbon on the dienophile with the higher LUMO concentration. Are your "predictions" consistent with the results of the transition-state calculations? Are any changes in regioselectivity resulting from BF_3 complexation consistent with the calculations?

There are many synthetic applications of Lewis acid catalyzed Diels-Alder reactions, and several have been presented previously in this chapter. Formation of **69** in Sect. 11.4.C.ii and **98** in Sect. 11.5.A are two examples. Another example is taken from the synthesis of the ABC ring of micrandilactone A by Chen, Yang and co-workers,¹⁴⁰ in which *E*-alkene **118** reacted with 1,3-butadiene **119** in the presence of the titanium tetrachloride bis(tetrahydrofuran) complex to give a 79% yield of **120**.



11.6.B. Rate Enhancement in Aqueous Media

For a long time, solvent polarity was believed to have no effect on the course of a Diels-Alder reaction. Berson, however, showed a clear relationship between the endo/exo product ratio

^{140.} Zhang, Y.-D.; Tang, Y.-F.; Luo, T.-P.; Shen, J.; Chen, J.-H.; Yang, Z. Org. Lett. 2006, 8, 107.

and solvent polarity in the Diels-Alder reaction of cyclopentadiene and acrylates.¹⁴¹ A patent by Hopff and Rautenstrauch in 1939¹⁴² reported the first water accelerated reaction when they showed that yields in the Diels-Alder reaction were enhanced in aqueous detergent solutions. In 1980, Breslow showed there was a hydrophobic acceleration for an intermolecular Diels-Alder reaction in which cyclopentadiene reacted with methyl vinyl ketone to give **121**.¹⁴³ When non-polar compounds are suspended in water their relative insolubility causes them to associate, diminishing the water-hydrocarbon interfacial area (a **hydrophobic effect**). This association is greater in water than in methanol, which brings the reactive partners into close proximity, increasing the rate of reaction. Any additive that increases the hydrophobic effect will increase the rate, as shown in Table 11.4¹⁴³ for the preparation of **121**. Lithium chloride (LiCl) increases

 Table 11.4.
 Hydrophobic Effects in the Diels-Alder Reaction of Cyclopentadiene and Methyl Vinyl Ketone in Aqueous Media

$ + \underbrace{\bigcirc}_{Me} \xrightarrow{additive}_{20^{\circ}C} \xrightarrow{O}_{121} \underbrace{\bigcirc}_{Me} $									
Solvent isooctane methanol water	<u>Additive</u>	<u>k2x10⁵ M⁻¹ s⁻¹</u> 5.94 75.5 4,410	<u>Solvent</u>	Additive LiCl (NH ₂) ₃ C ⁺ Cl ⁻ β-cyclodextrin α-cyclodextrin	$\frac{k_2 x 10^5 M^{-1} s^{-1}}{10,800}$ 4,300 10,900 2,610				
[Reprinted with permission from Rideout, D.; Breslow, R. J. Am. Chem. Soc. 1980 , 102, 7816. Copyright © 1980 American Chemical Society.]									

the hydrophobic effect by salting-out nonpolar material, but guanidinium chloride decreases hydrophobic interactions. β -Cyclodextrin (cycloheptaamylose) possesses a hydrophobic cavity and if the reactive intermediates can fit within this cavity there is a significant rate enhancement. The smaller α -cyclodextrin cannot accommodate the reactive species, and the rate is significantly diminished. Microwave-assisted Diels-Alder reactions have been reported in both water and in ionic liquid media using Lewis acid catalysts.¹⁴⁴

There are many examples of Diels-Alder reactions that exploit this rate enhancement effect. Grieco and co-worker's synthesis of quassinoids led to the reaction of **122** and **123**, in benzene at 25°C, which gave a 1:1.18 mixture of **124** and **125** in 52% yield but required a reaction time of 288 hours.¹⁴⁵ When the same reaction was done in water, an 82% yield was obtained (1.3:1

^{141.} Berson, J.A.; Hamlet, Z.; Mueller, W.A. J. Am. Chem. Soc. 1962, 84, 297.

^{142.} Hopff, H.; Rautenstrauch, C.W. U.S. Patent 2,262,002, 1939 [Chem. Abstr., 36: 10469, 1942.

^{143.} Rideout, D.; Breslow, R. J. Am. Chem. Soc. 1980, 102, 7816.

^{144.} Chen, I.-H.; Young, J.-N.; Yu, S.J. Tetrahedron 2004, 60, 11903.

^{145.} Grieco, P.A.; Garner, P.; He, Z. Tetrahedron Lett. 1983, 24, 1897

124/125) after 168 hours. Diels-Alder cyclization with the free acid rather than the ester, in water, gave an 85% yield (1.5:1 **124/125**) in 17 hours. Similar reaction in 1:1 aqueous methanol gave a quantitative yield after 97 hours (1:1.25 **124/125**). When the sodium salt of the acid was used, a quantitative yield was obtained in 5 hours (3:1 **124/125**).¹⁴⁵ In all cases, the reactions were carried out at room temperature with a fivefold excess of diene over dienophile. Breslow et al. showed that addition of guanidinium perchlorate to a Diels-Alder reaction slowed the reaction, which was taken as evidence that the special ability of water to enhance the rate of the Diels-Alder reaction was due to a hydrophobic effect.¹⁴⁶



An aqueous environment creates a medium where the "reactants orient themselves within a micelle, thereby increasing their effective molarity and, consequently, the rate."¹⁴⁷ Liotta and co-workers, however, point out that reaction of 2,6-dimethylbenzoquinone (**127**) and diene carbonate **126** showed no rate enhancement in water relative to the same reaction in benzene. The carbonate was essentially insoluble in water and rate enhancement requires at least partial solubility of the diene and/or dienophile in the aqueous medium. Other solvents with the ability to enhance molecular aggregation while maintaining the solubility of the reactants showed an increase in rate. Ethylene glycol, for example, showed a large rate enhancement (relative to methanol) for the reaction of **126** and **127** to give a quantitative yield of **128**. The influence of several solvents (relative dielectric constants and relative rates with reaction in benzene as the standard) was examined for several substrates.¹⁴⁷ Liotta explains this effect by comparing **129** and **130** in Figure 11.12,¹⁴⁷ where the π -stacked arrangement in the micelle (**129**) assumes a smaller volume and is probably preferred. The larger micelle volumes in the end-on arrangement (**130**) will disrupt hydrogen bonding and be higher in energy. The smaller volume of **129** will retain the maximum hydrogen bonding and minimize disruption.¹⁴⁷



^{146.} Breslow, R.; Maitra, U.; Rideout, D. Tetrahedron Lett. 1983, 24, 1901.

^{147.} Dunams, T.; Hoekstra, W.; Pentaleri, M.; Liotta, D. Tetrahedron Lett. 1988, 29, 3745.



Figure 11.12. π Stacked versus end-on arrangement in the micelle of aqueous Diels-Alder reactions. [Reprinted with permission from Dunams, T.; Hoekstra, W.; Pentaleri, M.; Liotta, D. *Tetrahedron Lett.* **1988**, 29, 3745, Copyright 1988, with permission from Elsevier Science.]

MOLECULAR MODELING: Selectivity in Cycloaddition of Quinone Carbonate

Cycloaddition of dienyl carbonate **126** with quinone **127** can lead to four possible products (*syn* and *anti* orientation of OCO_2Me and the quinone methyl groups, each with two *endo*-regioisomers and two *exo*-regioisomers). Previously, anticipating the regiochemical preference for cycloaddition reactions has relied on aligning the largest orbital coefficients associated with the HOMO on the diene and LUMO on the dienophile. While such procedure may be satisfactory where the positions on the diene and dienophile are markedly different, it is not reliable where the differences are subtle. Consider cycloaddition of **126** and **127**, leading to four possible products. The molecular orbitals of the reactants (especially 127) are delocalized, and seems unlikely that the observed product **128** could have been anticipated from examination of their orbital coefficients.

Calculations offer a more reliable method for determining the regiochemical preferences. Transition states corresponding to each possible product are generated and their energies compared. The lowest-energy transition state leads to the dominant product. Examine the transition states leading to the four products. From left to right and top to bottom on screen, these correspond to the *syn-endo*, *anti-endo*, *syn-exo* and *anti-exo* products. Can you pick out which among them is "least crowded"? If you can, is this the transition state leading to **128**?

All four transition states have very similar energies. In accord with observation, the transition state leading to the *syn-endo* product, **128**, is favored and leads to 82% of the total at room temperature. *Anti-endo* and *syn-exo* products each account for 9% and the *anti-exo* product for 2%. All four products arise from the same reactants, meaning that differences in the energies of the transition states are the same as differences in activation energies. Therefore, the kinetic produce is that which follows from the lowest energy transition state.

In summary, while comparison of the geometries of transition states for related reactions looking for which is "least crowded" may not always lead to a clear assignment of the favored product, comparison of activation energies will likely provide an reliable indicator.

Grieco and Larsen also showed that iminium salts such as **131**, formed by reaction of an amine and formaldehyde (sec. 4.4) reacted with cyclopentadiene in aqueous media to give a

near-quantitative yield of the Diels-Alder adduct.¹⁴⁸ An internal Diels-Alder reaction was also possible¹⁴⁸ (sec. 11.8).

$$Ph \longrightarrow_{NH_{2} \bullet HCl} \xrightarrow{HCHO} \begin{bmatrix} Ph \longrightarrow_{+ N = CH} \\ H & Cl^{-} \end{bmatrix} \xrightarrow{\swarrow} \swarrow_{N} \xrightarrow{N} Ph$$

$$131$$

The use of highly polar media such as water clearly assists the Diels-Alder reaction, and similar rate enhancement has been observed in other reactions. Grieco et al. showed that 5.0 M lithium perchlorate in diethyl ether is an effective medium for these reactions.¹⁴⁹ In a synthesis of (–)-elisapterosin B,¹⁵⁰ Rychnovsky and Kim used the reagent to facilitate the Diels-Alder reaction of diene **132** and quinone **133**. The two products were formed in 75% yield, as a 1.7:1 mixture of **134** and **135**.



When highly polar media such as this are used, weak acids become strong acids, and protonation of dienes has been observed in intramolecular reactions, that can lead to diene isomerization. Such isomerization may be competitive with cycloaddition.¹⁵¹ Grieco and Kaufman found that for such reactions, water is the polar medium of choice.¹⁵¹ Recently, Augé found that lithium trifluoromethane-sulfonate in ether or acetonitrile is a useful substitute for lithium perchlorate in cycloaddition reactions.¹⁵²

11.6.C. Rate Enhancement under High-Pressure Conditions

The rate of Diels-Alder reactions can be increased by the application of high pressure. High pressure is but one of a number of methods for activating reactions, including microwave and

^{148.} Larsen, S.D.; Grieco, P.A. J. Am. Chem. Soc. 1985, 107, 1768.

For examples, see (a) Grieco, P.A.; Nunes, J.J.; Gaul, M.D. J. Am. Chem. Soc. 1990, 112, 4595; (b) Grieco, P.A.; Moher, E.D. Tetrahdron Lett. 1993, 34, 5567; (c) Grieco, P.A.; Beck, J.P. Ibid. 1993, 34, 7367; (d) Grieco, P.A.; Beck, J.P.; Handy, S.T.; Saito, N.; Daeuble, J.F.; Ibid. 1994, 35, 6783; (e) Grieco, P.A.; Piñeiro-Nuñez, M.M. J. Am. Chem. Soc. 1994, 116, 7606; (f) Grieco, P.A.; Dai, Y. J. Am. Chem. Soc. 1998, 120, 5128; (g) Grieco, P.A.; Kaufman, M.D. Tetrahedron Lett. 1999, 40, 1265.

^{150.} Kim, A.I.; Rychnovsky, S.D. Angew. Chem. Int. Ed. 2003, 42, 1267.

^{151.} Grieco, P.A.; Kaufman, M.D. J. Org. Chem. 1999, 64, 6041.

^{152.} Augé, J.; Gil, R.; Kalsey, S.; Lubin-Germain, N. Synlett 2000, 877.

ultrasound enhancement.¹⁵³ Microwave-assisted Diels-Alder reactions have also been shown to be more effective when pressurized reaction vessels are used.¹⁵⁴ An early example by Dauben and Kozikowski¹⁵⁵ demonstrated that methyl 1-pentadienoate reacted with **136** to give **137** in 88% yield. Matsumoto and co-workers reviewed applications of high-pressure techniques to organic synthesis,¹⁵⁶ and also published a monograph.¹⁵⁷ The second part of the review^{156B} deals with high-pressure pericyclic reactions, including Diels-Alder reactions.



The thermodynamic properties of solutions are well known, and the rate of a reaction can be expressed in terms of the activation volume, ΔV^{\ddagger}

$$\frac{\delta \ln k}{\delta p} = \frac{V^{\ddagger}}{RT} \qquad 11.4$$

"The activation volume is the difference in partial molal volume between the transition state and the initial state. From a synthetic point of view this could be approximated by the molar volume."¹⁵⁶ Equation (11.4) suggests that the rate of the reaction will be accelerated with increasing pressure if the volume of activation is negative. As the pressure increases, the value of ΔV^{\ddagger} decreases and the system does not strictly obey equation (11.4) > 10 kbar (1 bar = 0.986924 atm. = 1.1019716 kg cm⁻²). Considerable information has been collected concerning ΔV^{\ddagger} , principally from work by le Noble.¹⁵⁸ If the transition state of a reaction involves bond formation, concentration of charge, or ionization, a negative volume of activation often results. Cleavage of a bond, dispersal of charge, or neutralization of the transition state and diffusion control lead to a positive volume of activation. Matsumoto summarizes the reactions for which rate enhancement is expected at high pressure.¹⁵⁶ (1) Reactions in which the molecularity number (number of molecules) decreases when starting materials are converted to products: cycloadditions, condensations. (2) Reactions that proceed via cyclic transition states: Claisen and Cope rearrangements (sec. 11.12.D and 11.11.C, respectively). (3) Reactions with dipolar transition states: **Menschutkin reaction**¹⁵⁹ (tertiary amines with alkyl halides to produce

- 155. Dauben, W.G.; Kozikowski, A.P. J. Am. Chem. Soc. 1974, 96, 3664.
- 156. (a) Matsumoto, K; Sera, A.; Uchida, T. Synthesis 1985, 1; (b) Matsumoto, K.; Sera, A. Ibid. 1985, 999
- 157. Matsumoto, K.; Morris, A.R. Organic Synthesis at High Pressure, Wiley, New York, 1991.
- 158. (a) le Noble, W.J. Progr. Phys. Org. Chem. 1967, 5, 207; (b) Isaacs, N.S. Liquid Phase High Pressure Chemistry, Wiley, Chichester, 1981; (c) Asano, T.; le Noble, W.J. Chem. Rev. 1978, 78, 407.
- (a) Menschutkin, N. Z. Physik. Chem. 1890, 5, 589; (b) Idem Ibid. 1890, 6, 41; (c) Ingold, C.K. Structure and Mechanism in Organic Chemistry, 2nd Ed., Cornell Univ. Press, New York, 1969, p 435; (d) The Merck Index, 14th ed., Merck &Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-60.

^{153.} Jenner, G. Tetrahedron 2002, 58, 5185.

^{154.} Kaval, N.; Dehaen, W.; Kappe, C.O.; Van der Eycken, E. Org. Biomol. Chem. 2004, 2, 154.

quaternary ammonium halides), electrophilic aromatic substitution. (4) Reactions with steric hindrance.

Table 11.5¹⁵⁶ shows the variation of rate constants with pressure. Many high-pressure reactions are done neat, but if a solvent is used, the influence of pressure on that solvent is important. The melting point generally increases at elevated pressures, and this influences the viscosity of the medium (the viscosity of liquids increases approximately two times per kilobar increase in pressure). Controlling the rate of diffusion of reactants in the medium is also important, leading to another influence of high pressure on reactivity.^{156,160} In most reactions, pressure is applied (5-20 kbar) at room temperature and then the temperature is increased until reaction takes place. The temperature is lowered and the pressure is reduced to isolate the products.

∆V [‡]	Temperature							
(<u>cm</u> ³ <u>mol</u> ⁻¹)	(° <u>C</u>)	<u>5 kbar</u>	<u>10 kbar</u>	<u>15 kbar</u>	<u>20 kbar</u>	<u> 30 kbar</u>	<u>50 kbar</u>	
-10	25	7.5	57	430	3200	1.8 x 10 ⁵	7.5 x 10 ⁸	
	50	6.4	41	270	1700	$7.1 \ge 10^4$	1.5 x 10 ⁸	
	100	5.0	25	130	630	$1.6 \ge 10^4$	1.2 x 10 ⁷	
		(-5)	(-10)	(-15)	(-20)	(-30)	(-50)	
-20	25	57	3200	1.8 x 10 ⁵	$1.0 \ge 10^7$	3.3 x 10 ¹⁰	5.6 x 10 ¹⁷	
	50	41	1700	$7.1 \ge 10^4$	2.9 x 10 ⁶	5.0 x 10 ⁹	2.4 x 10 ¹⁶	
	100	25	630	1.6 x 10 ⁴	$4.0 \ge 10^5$	$2.5 \ge 10^8$	1.5 x 10 ¹⁴	
		(-10)	(-20)	(-30)	(-40)	(-60)	(-100)	
-30	25	430	1.8 x 10 ⁵	7.7 x 10 ⁷	$3.3 \ge 10^{10}$	6.0 x 10 ¹⁵	4.2 x 10 ²⁶	
	50	270	7.1 x 10 ⁴	1.9 x 10 ⁷	5.0 x 10 ⁹	$3.6 \ge 10^{14}$	$3.7 \ge 10^{24}$	
	100	130	$1.6 \ge 10^4$	$2.0 \ge 10^6$	$2.5 \ge 10^8$	$4.0 \ge 10^{12}$	1.9 x 10 ²¹	
		(-15)	(-30)	(-45)	(-60)	(-90)	(-150)	
^a k_p = rate constant under high pressure; k_1 = rate constant at atmospheric pressure								
[Reprinted from Matsumoto, K; Sera, A.; Uchida, T. Synthesis 1985, pp. 1. Copyright 1985 by Georg Thieme Verlag.]								

 Table 11.5.
 Variations of Rate Constants with Pressure

Diels-Alder reactions with furans can be very problematic due to the thermal sensitivity of the cycloadduct, and their tendency for cycloreversion. These problems are due to the strain inherent to the 7-oxabicycloheptane cycloadduct (**138**), as well as the aromatic character of the furan. Raising the pressure of the reaction to 13.5 to 15 kbar in dichloromethane as a solvent, leads to fast reactions and yields approaching those obtained with Lewis acid catalysts and long reaction times.¹⁵⁶ 2-Methylfuran is more reactive than furan but substituents on the alkene (dienophile) lower the yield of the cycloadduct, even under high pressure. One synthetic example is taken from Funk and Maeng's synthesis of fasicularin, in which diene **139** reacted

^{160.} Firestone, R.A.; Vitale, M.A. J. Org. Chem. 1981, 46, 2160.

with 140 in dichloromethane at 12 kbar to give a 93% yield of 141.¹⁶¹



Furan also reacted with benzoquinone (at 20 kbar) to give a 14% yield of the endo adduct and a 15% yield of the exo adduct, along with 71% of unreacted benzoquinone.¹⁶² Better results were obtained with functionalized furans such as **142**, which reacted with 4-methyl-2-cyclopentenone at 15 kbar to give a 1:2 mixture of **143/144** in 95% yield (after 2 days), in Ghosez' and co-worker's synthesis of polyfunctionalized cis-hydrindanones.¹⁶³ Thiophenes react with maleic anhydride under high pressure conditions, where it was observed that solventfree conditions led to a significant lowering of the requisite reaction pressure, improvement in yield of products, and allowed less reactive dienophiles such as methyl acrylate to be used.¹⁶⁴ 2-Pyrones are another candidate for high pressure reactions since the normal Diels-Alder reaction usually requires high temperatures, and the products often lose carbon dioxide in a retro-Diels-Alder reaction.¹⁶⁵



Pyridones react at high pressure to give the cycloadduct,¹⁶⁶ whereas heating at atmospheric pressure usually gives no reaction at all.¹⁶⁶ A variety of relatively unreactive dienes and/or dienophiles give enhanced yield of cycloadducts under pressure. Naphthalene reacted with maleic anhydride at 9.5 kbar and 100°C.¹⁶⁷ Acetaldehyde reacted with 1-methoxybutadiene

^{161.} Maeng, J.-H.; Funk, R.L. Org. Lett. 2002, 4, 331.

^{162.} Jurczak, J.; Koz'luk, T.; Filipek, S.; Eugster, C.H. Helv. Chim. Acta 1983, 66, 222.

^{163.} Trembleau, L.; Patiny, L.; Ghosez, L. Tetrahedron Lett. 2000, 41, 6377.

^{164.} Kumamoto, K.; Fukada, I.; Kotsuki, H. Angew. Chem. Int. Ed. 2004, 43, 2015.

^{165.} Pfaff, E.; Plieninger, H. Chem. Ber. 1982, 115, 1967.

^{166.} Gisby, G.P.; Royall, S.E.; Sammes, P.G. J. Chem. Soc. Chem. Commun. 1979, 501.

 ^{167. (}a) Jones, W.H.; Mangold, D.; Plieninger, H. *Tetrahedron* 1962, 18, 267; (b) Plieninger, H.; Wild, D.; Westphal, J. *Ibid.* 1969, 25, 5561.

(sealed tube, 160-180°C, 6 hours) to give only 2% of the dihydropyran cycloadduct.¹⁶⁸ When the reaction was done neat at 14 kbar and 80°C for 6 hours, 50% of pyran was obtained¹⁶⁸ and reaction in ether at 20 kbar (65°C, 5 hours)¹⁶⁹ gave a 62% yield of pyran. Dienamines reacted with conjugated esters at 13.9 kbar to give a 70% yield of an enamine cycloadduct.^{170,155}

Intermolecular Diels-Alder reactions have a large negative volume of activation¹⁷¹ (~-25 to -45 cm³ mol⁻¹) and a large negative volume of reaction. The activation volume for intramolecular Diels-Alder reactions was measured as -25 cm³ mol⁻¹.¹⁷² The effects on the intermolecular Diels-Alder can be dramatic, but intramolecular Diels-Alder reactions do not always respond to high pressure.^{155,170} There are exceptions.¹⁷³ In one example, **145** could be cyclized to give a 1:1 mixture of **146/147** in refluxing toluene, at ambient pressure.¹⁷⁴ In order to suppress side reactions, a small amount of the radical scavenger BHT (2,6-di-*tert*-butyl-4-phenylphenol) was used. When done at 13 kbar in dichloromethane at room temperature, an 88% yield of a 1:2.3 mixture of **146/147** was obtained without the need for added BHT. It is noted that attempts to cyclize **145** using several different Lewis acids were not successful. Intramolecular Diels-Alder reactions will be discussed in Section 11.8.



A variation in this technique has recently been reported, although not necessarily using the high pressures described above. Diels-Alder reactions can be done under pressure in supercritical

^{168.} Makin, S.M.; El'yanov, B.S.; Raifel'd, Yu.E. Izv. Akad Nauk. SSSR Ser. Khim. 1976, 831 (Engl. p 810).

^{169.} Jurczak, J.; Chmielewski, M.; Filipek, S. Synthesis 1979, 41.

^{170.} Darling, S.D.; Subramanian, N. J. Org. Chem. 1975, 40, 2851.

 ^{171. (}a) vor der Brück, D.; Bühler, R.; Hück, C.-Ch.; Plieninger, H.; Weale, K.E.; Westphal, J.; Wild, D. Chem.-Ztg. 1970, 94, 183 [Chem. Abstr., 73:3128r 1970]; (b) McCabe, Jr.; Eckert, C.A. Acc. Chem. Res. 1974, 7, 251.
 172. Lawren N.S., der Berle, P.V. T. (abstr., 1970); (b) McCabe, Jr.; Eckert, C.A. Acc. Chem. Res. 1974, 7, 251.

^{172.} Isaacs, N.S.; der Beeke, P.V. Tetrahedron Lett. 1982, 23, 2147.

⁽a) Klärner, F.-G.; Diedrich, M.K.; Wigger, A.E. Chemistry under Extreme or Non-Classical Conditions, van Eldik, R.; Hubbard,. C.D. (Eds.), Wiley, New York, 1997, pp 103-161; (b) Jurczak, J.; Gryko, D.T. Chemistry under Extreme or Non-Classical Conditions, van Eldik, R.; Hubbard,. C.D. (Eds.), Wiley, New York, 1997, pp 163-188; (c) Ibata, T. Organic Synthesis at High Pressures, Matsumoto, K.; Archeson, R.M. (Eds), Wiley, New York, 1991, pp 213-285; (d) Uyehara, T.; Yamamoto, Y. Organic Synthesis at High Pressures, Matsumoto, K.; Archeson, R.M. (Eds), Wiley, New York, 1991, pp 409-422; (e) Diedrich, M.K.; Klärner, F.-G. J. Am. Chem. Soc. 1998, 120, 6212; (f) Ciobanu, M.; Matsumoto, K. Liebigs Ann.-Recl. 1997, 623.

^{174.} Plietker, B.; Seng, D.; Frölich, R.; Metz, P. Tetrahedron 2000, 56, 873.

carbon dioxide, although the synthetic application may be limited by slow reaction rates.¹⁷⁵ Addition of a Lewis acid can compensate, as illustrated by Kobayashi's use of scandium triflate^{176a} in the reaction of methyl vinyl ketone with 2-methyl-1,3-butadiene to give a 93:7 mixture of **148/149**. Rayner and co-workers had previously used scandium triflate in supercritical CO₂,^{176b} and reported that the maximum selectivity was obtained at a density of 1.12 g mL⁻¹.

11.7. HETEROATOM DIELS-ALDER REACTIONS

The Diels-Alder reaction is quite remarkable in its scope. One of the more attractive features is the ability to incorporate heteroatoms into either the diene, or the alkene unit, generating heterocyclic compounds. This section will examine several of the more useful variations.

11.7.A. Heteroatom Substituents

In previous sections, several examples were shown using alkoxydienes or alkoxyalkenes. Acyloxy dienes are very useful in organic synthesis. One example is Bohlmann and co-worker's synthesis of liglularone, which reacted acetoxydiene **150** with quinone **151** to give **152**.¹⁷⁷ An attractive feature of dienes that contain a vinyl ether or vinyl ester moiety is the facile hydrolysis of the cycloadduct (the vinyl ester unit in **152**) to give a ketone (see **153**). The hydrolysis of vinyl ethers was previously shown with the Birch reduction (sec. 4.9.E).



Danishefsky used a variety of silyloxybutadienes in Diels-Alder reactions¹⁷⁸ in place of alkoxy and acetoxy derivatives. Treatment of the resulting siloxy cycloadducts with fluoride ion (sec. 7.3.A.i) or simply with aqueous acid will generate an enol, which tautomerizes to the carbonyl under very mild conditions. In Nishida and co-worker's synthesis of (-)-nakadomarin A,¹⁷⁹

- 177. Bohlmann, F.; Förster, H.-J.; Fischer, C.H. J.L. Ann. Chem. 1976, 1487.
- 178. (a) Danishefsky, S. Acc. Chem. Res. 1981, 14, 400; (b) Idem Aldrichimica Acta 1986, 19, 59.
- 179. Ono, K.; Nakagawa, M.; Nishida, A. Angew. Chem. Int. Ed. 2004, 43, 2020.

⁽a) Renslo, A.R.; Weinstein, R.D.; Tester, J.W.; Danheiser, R.L. J. Org. Chem. 1997, 62, 4530; (b) Weinstein, R.D.; Renso, A.R.; Danheiser, R.L.; Harris, J.G.; Tester, J.W. J. Phys. Chem. 1996, 100, 12337; (c) Hyatt, J.A. J. Org. Chem. 1984, 49, 5097; (d) Paulaitis, M.E.; Alexander, G.C. Pure Appl. Chem. 1987, 59, 61; (e) Ikushima, Y.; Saito, N.; Arai, M. Bull. Chem. Soc. Jpn., 1991, 64, 282; (f) Isaacs, N.S.; Keating, N. J. Chem. Soc. Chem. Commun. 1992, 876.

^{176. (}a) Matsuo, J.-i.; Tsuchiya, T.; Odashima, K.; Kobayashi, S. Chem. Lett. 2000, 178; (b) Oakes, R.S.; Heppenstall, T.J.; Shezad, N.; Clifford, A.A.; Rayner, C.M. Chem. Commun. 1999, 1459.

154 reacted with diene **155** to give **156**. Subsequent reaction with trifluoroacetic acid gave a 52% overall yield of conjugated ketone **157**. Preparation of silyl enol ethers is usually easier than the preparation of the corresponding enol ether.¹⁸⁰ Diene **155** is a variation of the commercially available OSiMe₃ derivative (**159**, known as **Danishefsky's diene**).¹⁸¹ This diene, or analogs, have been very useful for a variety of natural product syntheses.^{151a} Many structural variations are possible for the alkoxybutadiene partner in the Diels-Alder reaction. Chiral heterosubstituted 1,3-butadienes¹⁸² are common in [4+2]-cycloaddition reactions and chiral dienophiles are used. Avenoza, Peregrina and co-workers used an asymmetric hetero-Diels-Alder reaction in a synthesis of carbacephams.¹⁸³ Chiral non-racemic imine **158**¹⁸⁴ reacted with Danishefsky's diene to give a 17:83 mixture of **160:161**, in 65% yield. Chiral Diels-Alder reactions will be discussed in section 11.9.



It is clear from these examples that oxygenated dienes are convenient and useful precursors to cyclohexenones and 7-oxabicycloheptane derivatives. Typical disconnections for oxygenated dienes are

^{180. (}a) Stork, G.; Hudrlik, P. J. Am. Chem. Soc. 1968, 90, 4462; (b) House, H.O.; Czuba, L.; Gall, M.; Olmstead, H.D. J. Org. Chem. 1969, 34, 2324; (c) House, H.O.; Gall, M.; Olmstead, H.D. Ibid. 1971, 36, 2361.

^{181. (}a) Danishefsky, S.; Kitahara, T.; Schuda, P.F.; Etheredge, S.J. J. Am. Chem. Soc. 1976, 98, 3028; (b) Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P.F. Ibid. 1976, 98, 6715; (c) Danishefsky, S.; Schuda, P.F.; Kitahara, T. Etheredge, S.J. Ibid. 1977, 99, 6066; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, p. 753.

^{182.} Barluenga, J.; Suárez-Sobrino, A.; López, L.A. Aldrichimica Acta 1999, 32, 4.

^{183.} Avenoza, A.; Busto, J.H.; Cativiela, C.; Corzana, F.; Peregrina, J.M.; Zurbano, M.M.J. Org. Chem. 2002, 67, 598.

^{184. (}a) Langenbeck. W.; Gödde, O.; Weschky, L.; Schaller, R. *Chem. Ber.* 1942, 75, 232; also see (b) Hünig, S.; Kahanek, H. C. *Ibid.* 1957, 90, 238; (c) Farmer, M.L.; Billups, W.E.; Greenlee, R.E.; Kurtz, A.N. J. Org. *Chem.* 1966, 31, 2885; (d) Mannich, C.; Handke, K.; Roth, K. *Chem. Ber.* 1936, 69, 2112.



11.7.B. Amino and Amido Dienes

Azadienes (amino or amido dienes) constitute another important class of hetero-substituted dienes. There are four major types, amino dienes such as 162, amido dienes such as 163, carbamoyl dienes such as 164, and pyrrole derivatives such as 165. Both 1- and 2-substituted aminodienes are possible, and they function as diene partners in Diels-Alder reactions.



Enamines have been used as dienophiles in previous examples. There are a few examples of Diels-Alder reactions with 1-(dialkylamino)-1,3-butadienes.¹⁸⁴ It is noted that a density functional study of the Diels-Alder reaction of 1,2-diaza-1,3-butadiene with alkenes showed the transition state to be concerted, but asynchronous.¹⁸⁵ The allylic amine cycloadducts of this reaction show a propensity for elimination, and this has led to the use of dienyl amides (163) and carbamates (164), whose cycloadducts are significantly more stable and easier to isolate.¹⁸⁶ The conversion of 70 to 71 in Section 11.4.C.iii used a diene of this type (see above). In another example, Oppolzer et al. showed that 166 reacted with methyl acrylate to give a 73% yield of 167 and 18% of 168.¹⁸⁷ The endo- (cis-) selectivity is apparent in this example and is general for this class of dienes. Amido dienes such as 166 can be prepared by reaction of conjugated aldehydes such as crotonaldehyde with an amine, a base, and an acid chloride.¹⁸⁸ In a synthesis of asparagamine A,¹⁸⁹ Overman and co-worker's showed that pyrrole 169 reacted with the nitro-acrylate shown to give 170, which was hydrogenated to give 171 in 73% yield. Similarly, Overman prepared dienyl carbamate 172 via a Curtius rearrangement¹⁹⁰ (a thermal rearrangement of a diazoketone to an isocyanate; dienyl azido ketone 172 \rightarrow 173; see sec.

- 186. Smith, M.B. Org. Prep. Proceed. Int. 1990, 22, 315.
- 187. Oppolzer, W.; Bieber, L.; Francotte, E. Tetrahedron Lett. 1979, 4537.
- (a) Oppolzer, W.; Fröstl, W. Helv. Chim. Acta 1975, 58, 587; (b) Oppolzer, W.; Bieber, L.; Francotte, E. Tetrahedron Lett. 1979, 981.
- Brüggemann, M.; McDonald, A.I.; Overman, L.E.; Rosen, M.D.; Schwink, L. Scott, J.P. J. Am. Chem. Soc. 2003, 125, 15284.
- 190. (a) Curtius, T. J. Prakt. Chem. 1894, 50, 275; (b) Smith, P.A.S. Org. React. 1946, 3, 337; (c) Saunders, J.H.; Slocombe, R.J. Chem. Rev. 1948, 43, 203.

^{185.} Avalos, M.; Babiano, R.; Clemente, F.R.; Cintas, P.; Gordillo, R.; Jiménez, J.L.; Palacios, J.C. J. Org. Chem. 2000, 65, 8251.

2.11.C). Heating with benzyl alcohol gave carbamate **174**.¹⁹¹ Overman and co-workers also found thermolysis of trichloroacetimidic esters of propargyl alcohols generated trichloromethyl dienyl carbamates.¹⁹²,¹⁹³ Dienyl carbamate reacted with styrene to give a quantitative yield of a mixture of **175** and **176** in a 93:7 ratio.¹⁹⁴ 1-Amino-3-siloxy-1,3-butadienes also react with unactivated aldehydes under mild conditions, at room temperature and in the absence of Lewis acids.¹⁹⁵ Dienyl lactams such as **177** have also been prepared and shown to undergo Diels-Alder reactions.¹⁹⁶ The same ortho and endo selectivity that was observed with dienyl amides was observed when *N*-(1,3-butadienyl)-2-pyrrolidinone reacted with ethyl acrylate and other alkenes.^{196c} When chiral lactam **177** reacted with ethyl acrylate, Smith and co-workers showed that the cycloadduct was formed with excellent enantioselectivity.^{196d} Rawal and co-workers prepared **178**, and showed Diels-Alder reactions proceed in good yield and with reasonable stereoselectivity.¹⁹⁷



- 191. (a) Overman, L.E.; Taylor, G.F.; Jessup, P.J. *Tetrahedron Lett.* **1976**, 3089; (b) Overman, L.E.; Taylor, G.F.; Petty, C.B.; Jessup, P.J. *J. Org. Chem.* **1978**, *43*, 2164.
- 192. (a) Overman, L.E.; Clizbe, L.A. J. Am. Chem. Soc. 1976, 98, 2352; (b) Overman, L.E. Ibid. 1976, 98, 2901.
- 193. Overman, L.E.; Clizbe, L.A.; Freerks, R.L.; Marlowe, C.K. J. Am. Chem. Soc. 1981, 103, 2807.
- 194. (a) Overman, L.E.; Freerks, R.L.; Petty, C.B.; Clizbe, L.A.; Ono, R.K.; Taylor, G.F.; Jessup, P.J. *J. Am. Chem. Soc.* **1981**, *103*, 2816; (b) Overman, L.E.; Taylor, G.F.; Houk, K.N.; Domelsmith, L.N. *Ibid.* **1978**, *100*, 3182.
- 195. (a) Huang, Y.; Rawal, V.H. Org. Lett. 2000, 2, 3321; (b) Huang, Y.; Iwama, T.; Rawal, V.H. J. Am. Chem. Soc. 2000, 122, 7843.
- 196. (a) Murata, K.; Terada, A. Bull Chem. Soc. Jpn. 1967, 40, 414; (b) Terada, A.; Murata, K. Ibid. 1967, 40, 1644; (c) Zezza, C.A.; Smith, M.B. J. Org. Chem. 1988, 53, 1161; (d) Menezes, R.F.; Zezza, C.A.; Sheu, J.L.; Smith, M.B. Tetrahedron Lett. 1989, 30, 3295.
- 197. Janey, J.M.; Iwama, T.; Kozmin, S.A.; Rawal, V.H. J. Org. Chem. 2000, 65, 9059.


There are two other classes of dienyl lactams that have been used synthetically, *N*-alkyl-2-pyridones (**179**), and *N*-acyl-1,2-dihydropyridines (**180**). Pyridones tend to be relatively unreactive, requiring high temperatures, often giving low yields of the cycloadduct.¹⁹⁸ *N*-Acyl pyrrole derivatives¹⁹⁹ also function as diene partners in the Diels-Alder reaction.

Nitrogen containing dienes lead to useful synthetic disconnections such as



11.7.C. Heteroatom Dienes and Heteroatom Alkene Dienophiles

Heteroatoms can be incorporated into the π framework of either the alkene partner or the diene partner of Diels-Alder reactions. This section will focus on two structural types that function as dienophiles: ketones or aldehydes, and imines (**181**). We will also focus on three types that function as dienes: conjugated carbonyls (**182**), 1-azadienes (**183**), and 2-azadienes (**184**). The use of heteroatom dienes and alkenes in organic synthesis was thoroughly reviewed by Boger and Weinreb,²⁰⁰ and by Fringuelli and Taticchi.²⁰¹



11.7.C.i. Aldehydes and Ketones. Most reactions that use carbonyl compounds as dienophiles involve aldehydes, which are more reactive than ketones. Hetero-Diels-Alder reactions of ketones are known, however.²⁰² Simple aldehydes and ketones do not react very well in

202. Jørgensen, K.A. Eur. J. Org. Chem. 2004, 2093.

^{198.} Raucher, S.; Lawrence, R.F. Tetrahedron Lett. 1983, 24, 2927.

^{199.} Groves, J.K.; Cundasawmy, N.E.; Anderson, H.J. Can. J. Chem. 1973, 51, 1089.

^{200.} Boger, D.L.; Weinreb, S.M. Hetero Diels-Alder Methodology in Organic Synthesis, Academic Press, San Diego, 1987.

^{201.} Fringuelli, F.; Taticchi, A. Dienes in the Diels Alder Reaction, Wiley, New York, 1990.



uncatalyzed reactions,²⁰³ although electrondeficient aldehydes and ketones are good partners. Chloral reacts with cyclohexadiene to give **185**.²⁰⁴ Glyoxalates²⁰⁵ (RO₂CCHO) also add to dienes.

The carbonyl moiety of electron deficient ketones functions as a dienophile,^{206a} but ketone dienophiles may require elevated temperatures and or high pressure to obtain good reactivity.²⁰⁶ Unactivated ketones react in hydrogen bond-promoted reactions²⁰⁷ with activated conjugated dienes.²⁰⁸

As mentioned, relatively simple aliphatic and aromatic aldehydes are unreactive except with very reactive dienes, and the reaction usually requires Lewis acid catalysis.²⁰⁹ Danishefsky's

diene reacts with aldehydes to give pyrones.²¹⁰ A synthetic example is the reaction of Danishefsky's diene (**159**) with **158** shown above,¹⁸¹ catalyzed by diethyl aluminum chloride. In Rainier



and co-worker's synthesis of the hemibrevetoxin B ring system,²¹¹ diene **155**, which is obviously related to Danishefsky's diene, reacted with *O*-benzyl 4-hydroxybenzaldehyde in the presence of zinc chloride to give **186** in 92% yield. Pyrones and pyrans are particularly useful for the preparation of acyclic precursors to macrocyclic antibiotics. Exploiting the selectivity inherent in the cyclic pyran (sec. 6.5) controls the stereochemistry of the highly oxygenated acyclic fragment.^{212,213} The disconnection is

- 203. (a) Tietze, L.F.; Kettschau, G. Top. Curr. Chem. 1997, 189, 1; (b) Kumar, A. Chem. Rev. 2001, 101, 1; (c) Jørgensen, K.A. Angew. Chem. Int. Ed. 2001, 39, 3558.
- 204. (a) Begley, M.J.; Benner, J.P.; Gill, G.B. J. Chem. Soc. Perkin Trans. 1 1981, 1112; (b) Smushkevich, Y.I.; Belov, V.N.; Kleev, B.V.; Akimova, A.Y. Zh. Org. Khim. 1967, 3, 1036 (Engl. p 997); (c) Dale, W.J.; Sisti, A.J. J. Org. Chem. 1957, 22, 449.
- 205. (a) Kanowal, A.; Jurczak, J.; Zamojski, A. *Rocz. Chem.* 1968, 42, 2045 [*Chem. Abstr.* 71: 3209b, 1969];
 (b) Zamojski, A.; Konowal, A.; Jurczak, J. *Ibid.* 1970, 44, 1981 [*Chem. Abstr.*, 75: 35008j, 1971];
 (c) Yablonovskaya, S.D.; Shekhtman, N.M.; Antonova, N.D.; Bogatkov, S.V.; Makin, S.M.; Zefirov, N.S. *Zh. Org. Khim.* 1970, 6, 871 (Engl. p 871).
- 206. (a) Daniewski, W.M.; Kubak, E.I.; Jurczak, J. J. Org. Chem. 1985, 50, 3963; (b) Bonjouklian, R.; Ruden, R.A. Ibid. 1977, 42, 4095.
- 207. Huang, Y.; Rawal, V.H. J. Am. Chem. Soc. 2002, 124, 9662.
- 208. Jørgensen, K.A. Eur. J. Org. Chem. 2004, 2093.
- 209. Jurczak, J.; Golebiowski, A.; Rahm, A. Tetrahedron Lett. 1986, 27, 853.
- (a) Reference 200, p 108; (b) Danishefsky, S.; Kerwin Jr., J.F.; Kobayashi, S. J. Am. Chem. Soc. 1982, 104, 358; (c) Danishefsky, S.; Kerwin Jr., J.F. J. Org. Chem. 1982, 47, 3183; (d) Danishefsky, S.; Webb II, R.R. Ibid. 1984, 49, 1955.
- 211. Rainier, J.D.; Allwein, S.P.; Cox, J.M. Org. Lett. 2000, 2, 231.
- (a) Danishefsky, S.; Pearson, W.H.; Harvey, D.F. J. Am. Chem. Soc. 1984, 106, 2456; (b) Kishi, Y. Pure Appl. Chem. 1981, 53, 1163.
- 213. Danishefsky, S.J. Aldrichimica Acta 1986, 19, 59 (see p 62).

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11.7.C.ii. Imines. Imines are used less often as dienophiles, but there are examples. Iminium salts are also known dienophiles. Simple imines are usually generated *in situ*, although more useful imines can be stabilized by the presence of electron-withdrawing groups on the nitrogen.

N-Tosyl imines such as **188** can be isolated. When **188** reacted with diene **187**, a 58% yield of tetrahydropyridine (**189**)²¹⁴ was obtained as part of Weinreb and Heintzelman's synthesis



of cylindrospermopsin. *N*-Acyl imines react similarly via the corresponding iminium salt. Bis(carbamates) are precursors to iminium salts that undergo Diels-Alder reactions.²¹⁵ Böhme and co-workers generated iminium salt **191** from chloromethylamine **190**, and subsequent reaction with 2,3-dimethylbutadiene gave **192** in 69% yield.²¹⁶ Grieco and co-worker's previously cited preparation and Diels-Alder reaction of iminium salt **126**, and the one derived from amine **128** in aqueous media, are related to this type of cycloaddition (sec. 11.6.B). Formation of nitrogen-containing cycloadducts via Diels-Alder reactions is an attractive route for the synthesis of alkaloids. Even simple imines can function as dienophiles. Danishefsky and Vogel reacted pyrroline (**193**) with siloxydiene **194** to give **195**, in a synthesis of ipalbidine.²¹⁷



A large variety of stable imines are easily prepared, making this technique valuable for the

^{214.} Heintzelman, G.R.; Weinreb, S.M. J. Org. Chem. 1996, 61, 4594.

^{215.} Merten, R.; Muller, G. Angew. Chem. 1962, 74, 866.

^{216.} Böhme, H.; Hartke, K.; Müller, A. Chem. Ber. 1963, 96, 607.

^{217.} Danishefsky, S.; Vogel, C. J. Org. Chem. 1986, 51, 3915.

preparation of nitrogen-containing cyclic and polycyclic molecules. Catalytic asymmetric hetero-Diels-Alder reactions using imines are known.²¹⁸ Two important disconnections for this type of Diels-Alder reactions are



11.7.C.iii. Nitroso-Type Compounds. Nitroso compounds (R–N=O) are dienophiles in Diels-Alder reactions, giving heterocyclic rings. In Kibayashi and co-worker's synthesis of fasicularin,^{219a} hydroxamic acid **196** was treated with tetrapropylammonium periodate and 9,10-dimethylanthracene to give transient acylnitroso compound **197**, and the resultant Diels Alder product **198** was formed in 84% yield. In this particular example, the Diels-Alder adduct essentially "protected" the acyl nitroso unit, which was used in a subsequent reaction.



11.7.C.iv. Conjugated Aldehydes and Ketones. Conjugated aldehydes and ketones function as dienes, in addition to their better known capabilities as dienophiles, as observed by Sherlin et al.²²⁰ Methyl vinyl ketone reacted with acrolein, but gave only 15% of a pyran cycloadduct in Mundy and co-worker's synthesis of brevicomin.²²¹ However, pyran formation by this reaction is well known,²²² and 2-substituted 3,4-dihydropyrans are the major products in almost all cases. This cycloaddition is obviously related to the reaction of aldehydes with dienes,

^{218.} For a review see Jørgensen, K.A. Angew. Chem. Int. Ed. 2000, 39, 3558.

 ⁽a) Abe, H.; Aoyagi, S.; Kibayashi, C. J. Am. Chem. Soc. 2000, 122, 4583. For the use of nitroso dienophiles for the synthesis of mannosidase and fucosidase inhibitors, see (b) Joubert, M.; Defoin, A.; Tarnus, C.; Streith, J. Synlett 2000, 1366. Also see (c) Bach, P.; Bols, M. Tetrahedron Lett. 1999, 40, 3461.

^{220.} Sherlin, S.M.; Berlin, A.Y.; Serebrennikova, T.A.; Rabinovich, R.F. J. Gen. Chem. USSR 1938, 8, 7, 22.

 ⁽a) Mundy, B.P.; Otzenberger, R.D.; DeBernardis, A.R. J. Org. Chem. 1971, 36, 2390, 3830; (b) Lipkowitz, K.B.; Mundy, B.P.; Geeseman, D. Synth. Commun. 1973, 3, 453; also see (c) Bhupathy, M.; Cohen, T. Tetrahedron Lett. 1985, 26, 2619.

^{222.} Desimoni, G.; Tacconi, G. Chem. Rev. 1975, 75, 651.

but provides pyran products with regiochemical differences relative to those prepared in sec. 11.7.C.i. Both Lewis acid catalysis and high-pressure techniques facilitate the cycloaddition. Electron deficient alkenes react as dienophiles with conjugated carbonyl derivatives,²²³ but electron rich alkenes (such as methyl vinyl ether) also react. An example is the reaction of the conjugated aldehyde **199** with the C=C unit of vinyl ether **200**, to give a 42% yield of **201** in Korte and co-worker's synthesis of *dl,iso*-iridomyrmecin.²²⁴ Boger and Weinreb.²²⁵ show several reactions of this type



The disconnection for this heteroatom Diels-Alder reaction is

11.7.C.v. Azadienes. Azadienes such as **182** and **183**²²⁶ are useful diene partners that can be used for the preparation of many heterocycles and alkaloids. The utility of 1-azadienes in the Diels-Alder reaction is limited by the fact that isomerization occurs to give a conjugated imine, probably via a proton transfer. An example is the equilibration of **202** and **203**. Addition of maleic anhydride to this mixture gave the Diels-Alder adduct **204**, derived from aminobutadiene **202**.²²⁷ Incorporation of tertiary alkyl substituents are used to stabilize the 1-azadiene. Even when isomerization is not possible, the aminobutadiene is relatively unreactive and the yields can be poor. An important side reaction is a competitive [2+2]-cycloaddition (sec. 11.10.A), further contributing to poor yields of the [4+2]-cycloadduct.^{228,229}

- 224. Korte, F.; Büchel, K.H.; Zschocke, A. Chem. Ber. 1961, 94, 1952.
- 225. Reference 200, pp 167-213.
- 226. For a review, see Behforouz, M.; Ahmadian, M. Tetrahedron 2000, 56, 5259.
- (a) Snyder, H.R.; Robinson Jr., J.C. J. Am. Chem. Soc. 1941, 63, 3279; (b) Snyder, H.R.; Cohen, H.; Tapp, W.J. Ibid. 1939, 61, 3560.
- 228. (a) Reference 200, p 242 and references 18a-c therein; (b) Taylor, E.C.; Eckroth, D.R.; Bartulin, J. J. Org. Chem. 1967, 32, 1899.
- 229. Garashchenko, Z.M.; Skvortsova, G.G.; Shestova, L.A. USSR Patent 370,208, 1973 [Chem. Abstr. 79: 31900d, 1973]

^{223.} Childers Jr., W.E.; Pinnick, H.W. J. Org. Chem. 1984, 49, 5276.



2-Azadienes such as **205** were prepared by Ghosez and co-workers and then reacted with conjugated alkynes [such as the methyl propiolate (**206**)] to give an initial cycloadduct **207**, but facile loss of dimethylamine led to aromatization and formation of pyridine derivative **208** as the final product.²³⁰ The previously noted azadiene-aminobutadiene rearrangement is impossible in **205**, and the dimethylamino moieties further stabilize the azadiene structure. Ghosez and co-workers also used 2-azadienes that were stabilized by the presence of silyloxy groups.²³⁰ Boger and Weinreb discuss several examples of 1- and 2-azadienes in Diels-Alder reactions.²³¹ Kende and co-workers used a less obvious azadiene in a synthesis of alantrypinone.²³² When 6H-pyrazino[2.1-b]quinazoline-6-one **209** was heated with 3-methyleneoxindole, a mixture of **210** and **211** was formed in 55% yield and 18% yield, respectively.



The synthetic utility of azadienes Diels-Alder reactions lies in the synthesis of heterocycles and alkaloids. Three disconnections related to this section are



^{230.} Sainte, F.; Serckx-Poncin, B.; Hesbain-Frisque, A.-M.; Ghosez, L. J. Am. Chem. Soc. 1982, 104, 1428.

232. Kende, A.S.; Fan, J.; Chen, Z. Org. Lett. 2003, 5, 3205.

^{231.} Reference 200, pp 239-358.

11.8. INTRAMOLECULAR DIELS-ALDER REACTIONS²³³

In previous discussions of the Diels-Alder reaction, the reactions of **34** and of **145** involved an intramolecular cycloaddition. The Diels-Alder reaction can occur intramolecularly if the diene

and alkene are connected by an intervening chain of atoms, illustrated by the conversion of **212** to **213**. This version of the reaction has become one of the most powerful synthetic methods (sec. 10.5.B.vi) for constructing cyclic compounds with high regio- and stereoselectivity.²³⁴ There is much interest



in intramolecular Diels-Alder reactions and many reviews, including those by Carlson in 1974,²³⁵ Oppolzer in 1977,²³⁶ Brieger and Bennett in 1980,²³⁷ Fallis in 1984²³⁸ and Smith in 1990.¹⁸⁶ Virtually all of the intermolecular reactions shown in previous sections have intramolecular analogs. The atoms that link the diene and alkene (the **tether**) can sometimes inhibit close approach of those moieties. Indeed, the ground state conformation of a molecule can greatly influence the reaction. Padwa and co-worker's studied the intramolecular Diels-Alder reaction



of *N*-alkenyl amidofurans²³⁹ and found that placement of a carbonyl in the tether can cause the molecule to adopt a conformation that is closer to the reactive conformation. The geometry of the diene and alkene (*E*) or (*Z*) also plays a role, which can be illustrated by comparing the intramolecular Diels-Alder reactions of **214A** and

215A. *trans*-Diene **214A** readily attains the proper geometry for reaction (see **214B**) with the methylene groups in the tether assuming a relatively normal conformation for a small ring.

cis-Diene **215A**, however, requires significant distortion of the methylene groups in the tether to even approach the proper orientation for the cycloaddition. In model **215B**, severe distortion is



apparent in the tether, where one or more bonds must be elongated to achieve the conformation shown. Such bond elongation and distortion of the tether is energetically unfavorable for this molecule.

^{233.} See Takao, K.-i.; Munakata, R.; Tadano, K.-i. Chem. Rev. 2005, 105, 4779.

^{234.} Fallis, A.G. Acc. Chem. Res. 1999, 32, 464.

^{235.} Carlson, R.G. Ann. Rep. Med. Chem. 1974, 9, 270.

^{236.} Oppolzer, W. Angew. Chem. Int. Ed. 1977, 16, 10 (see p 10-18).

^{237.} Brieger, G.; Bennett, J.N. Chem. Rev. 1980, 80, 63 (see p 67).

^{238.} Fallis, A.G. Can. J. Chem. 1984, 62, 183.

^{239.} Bur, S.K.; Lynch, S.M.; Padwa, A. Org. Lett. 2002, 4, 473.



The *length* of the tether is very important.^{240,241} Boeckman and Demko showed that Diels-Alder cyclization of **216** gave 50% of a 70:30 mixture (β H/ α H = cis/trans) of **217.**²⁴² Attempted cyclization of **218**, which has fewer carbons in the tether, gave no cyclized product. This latter example shows a preference for the transoid conformation and has a higher energy of activation for interconversion of the two rotamers than does **216**.^{242,243a}



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The influence of the tether length is particularly striking in the substituted cyclopentadienes examined by Stille and Grubbs.²⁴⁴ Each cyclopentadiene derivative is in equilibrium with three isomers, the 1-substituted, 2-substituted and 3-substituted cyclopentadienes. A two-carbon tether (n = 1), as in **219** \rightarrow **221**, gave 53% of **222** when heated in benzene.²⁴⁴ The 2-substituted derivative (**220**) and 3-substituted derivative (**223**) gave no cycloadduct (**223** and **224**, respectively, where n = 1), presumably due to the difficulty in forming the four-membered ring in **223**, and attaining the proper geometry for the bridgehead π bond in **224** (see **Bredt's rule** in sec. 6.6.A). The endo-transition state required to generate **222** is relatively easy to achieve. Adding one carbon to the tether (**219**, n = 2), however, and heating led to a 6.4:1

^{240.} Kraus, G.A.; Bougie, D.; Jacobson, R.A.; Su, Y. J. Org. Chem. 1989, 54, 2425.

^{241.} Tagmazyan, K.Ts.; Mkrtchyan, R.S.; Babayan, A.T. Zh. Org., Khim. 1974, 10, 1642. (Engl. p 1657).

^{242.} Boeckman Jr., R.K.; Demko D.M. J. Org. Chem. 1982, 47, 1789.

^{243. (}a) For a related reaction with furan derivatives, see Parker, K.A.; Adamchuck, M.R. *Tetrahedron Lett.* 1978, 1689; (b) Reference 80b, p 167.

^{244.} Stille, J.R.; Grubbs, R.H. J. Org. Chem. 1989, 54, 434.

mixture of **223** and **224** (n = 2).²⁴⁴ The cyclization of **219** \rightarrow **222** (n = 2) was *not* observed. The 2-substituted derivative gave the highest yield of cyclized product when n = 2.²⁴⁴ Adding a total of four carbons to the tether gave results similar to when n = 2 in **219-221**.²⁴⁴ These examples clearly show that the length and nature of the tether is important, and inspection of all possible transition states is essential for predicting the cycloadducts arising from intramolecular Diels-Alder reactions.

In addition to the problems concerning reactivity and the nature of the tether, at least two different regioisomers are possible for internal Diels-Alder reactions (**226** and **227** from **225**), depending on the orientation of the alkene as it approaches the diene. If the tether is short, only **227** is possible, but with longer tethers **226** can be a side product or even the major product. In Thomas and co-worker's studies²⁴⁵ on the synthesis of cytochalasin, an intramolecular Diels-Alder reaction of **228** gave a 27:5% mixture of **229** and **230**. In general, (*E*)-dienes do not give products such as **220**, although (*Z*)-dienes do. As the reactive termini approach, the alkene arm can assume an exo or an endo mode. The exo transition state leads to the trans-product, and the endo transition state leads to the cis product. The final outcome depends on the conformation assumed in the transition state, based on the structures of the reactive species (sec. 1.5.D).²³⁷ In general, the exo transition state is preferred.



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As mentioned previously, the length of the tether, reaction conditions and catalyst, if any, will influence the cis/trans ratio. Houk and co-workers compared the cyclization of trienes (231) with several tether lengths to give the bicyclic cycloadduct 232.²⁴⁶ The cis adduct was preferred except when n = 5 (to form a nine-membered ring). Gras initially reported that when

^{245.} Bailey, S.J.; Thomas, E.J.; Turner, W.B.; Jarvis, J.A. J. Chem. Soc. Chem. Commun. 1978, 474.

^{246.} Smith, D.A.; Sakan, K.; Houk, K.N. Tetrahedron Lett. 1986, 27, 4877.

n = 2 the trans product was preferred²⁴⁷ (later corrected), but Houk found that the cis product was preferred. When n = 4-7, the product yields were decreased, reflecting the difficulty in generating the transition state for an 8-11-membered ring in **232** (secs. 1.5.B,C, 6.6.B). There are many applications of the intramolecular Diels-Alder reaction to natural product synthesis. In a synthesis of sordaricin,²⁴⁸ Mander and Thomson stirred **233** at 40°C for 3 days, and obtained quantitative yield of **234**. Using an intramolecular Diels-Alder strategy that involved a transannular cyclization, Tadano and co-worker's converted **235** to **236**, in a synthesis of (+)-macquarimicin A.²⁴⁹



Table 11.6. Intramolecular Cycloaddition of Selected Trienes²⁵⁰

Me R 0 237 0	PhMe conditions	H = H = H = Me + H = H = H = H = H = H = H = H = H = H	$\begin{array}{c} H \stackrel{R}{\overline{}} H \stackrel{Me}{\overline{}} \\ H \stackrel{R}{\overline{}} H \stackrel{Me}{\overline{}} \\ H \stackrel{R}{\overline{}} \\ H \stackrel{R}{\overline{} \\ H \stackrel{R}{\overline{}} \\ H \stackrel{R}{\overline$		
<u>R</u>	Conditions	<u>%Yield</u>	<u>238:239</u>		
CO ₂ Et	200°C (3 h)	77	1:4		
CO ₂ Et	110°C (1 day)	58	1 : 1		
CO ₂ Et	SiO ₂ •Et ₂ AlCl	31	3 : 1		
CH ₂ OTBS	110°C (16 h)	0	1:1		
CH ₂ OTBS	SiO ₂ •Et ₂ AlCl	75	20:1		
[Reprinted with permission from Hart, D.J.; Li, J.; Wu, WL.; Kozikowski, A.P. J. Org. Chem. 1997, 62, 5023. Copyright © 1997 Amer. Chem. Soc.]					

^{247.} Gras, J.-L.; Bertrand, M. Tetrahedron Lett. 1979, 4549.

^{248.} Mander, L.N.; Thomson, R.J. Org. Lett. 2003, 5, 1321.

^{249.} Munakata, R.; Katakai, H.; Ueki, T.; Kurosaka, J.; Takao, K.; Tadano, K. J. Am. Chem. Soc. 2003, 125, 14722.

Even when a single substrate is used, the ratio of diastereomeric products can vary with reaction conditions. In Hart, Kozikowski and co-workers synthesis of (+)-himbeline and (+)-himbacine,²⁵⁰ **237** was cyclized to a mixture of **238** and **239** using the conditions in Table 11.6. At higher temperatures, the reaction favored **239** but with an acid promoter at lower temperatures, **238** was favored. When the ester group in **237** was changed to the reduced form (a TBS protected alcohol), heating to 110°C gave a 1:1 mixture whereas the acid promoted lower temperature reaction gave a 20:1 mixture favoring **238**.

MOLECULAR MODELING: Thermodynamic vs. Kinetic Control in Diels-Alder Reactions

The distribution of products for a reaction may reflect either their relative energies (*thermodynamic control*), or the relative energies of the transition states (*kinetic control*). High temperatures and long reaction times generally favor thermodynamic control, although in practice it is often difficult to say with certainty whether kinetics or thermodynamics is in control. On the other hand, quantum chemical calculations provide the means to access both relative product and transition state energies and, therefore, can provide an unambiguous account. A good example is provided by comparison of intramolecular Diels-Alder reactions for *E*-1,3,9-decatriene, which yields an equal amount of *cis* and *trans* products, and of its 3-methyl derivative, which shows a preference for a *cis* product.



Click on > to the right of the tab at the top of the screen and select *Continue* to bring up the modelbuilding palette. Build the *trans* product A for R = H and obtain the energy. Repeat the sequence (*click* on >, select *Continue*, build and obtain the energy) for the corresponding *cis* product B, and for the *trans* and *cis* products for R=Me. Are the calculated relative energies consistent with the experimental data? In particular, do you find that reaction of the unsubstituted compound occurs with little if any stereochemical preference, while that of the methyl substituted compound shows a modest preference for *exo* addition? Overall, do the calculations suggest that the reaction is or is not under thermodynamic control?

Click on the rightmost tab at the top of the screen to bring back the screen containing the transition state models that opened this problem. Shown are transition states for *exo* (left) and *endo* (right) cycloadditions of *E*-1,3,9-decatriene (top) and 3-methyl-*E*-1,3,9-decatriene (bottom). Calculated energies (not provided) for the *exo* and *endo* transition states for reaction of *E*-1,3,9-decatriene are nearly the same, suggesting that the reaction will produce an equal mixture of *trans* and *cis* products. On the other hand, calculations show that the *exo* transition state for reaction of 3-methyl-*E*-1,3,9-decatriene is 12 kJ/mol lower in energy than the corresponding *endo* transition state. This translates into a 96:4 *trans:cis* mixture (favoring for *exo* addition) at 358 K (160°C). These results are close to what is observed experimentally, and they support the notion that the reaction is kinetically controlled. Examine the individual transition state geometries. Can you find any evidence that reaction of the methyl-substituted triene should be more selective than the reaction of the unsubstituted compound?

^{250.} Hart, D.J.; Li, J.; Wu, W.-L.; Kozikowski, A.P. J. Org. Chem. 1997, 62, 5023

In the cyclization of dienyl amides, Oppolzer noted a difference in regiochemistry between dienes having the carbonyl *external to the ring being formed* $(240 \rightarrow 241)$,^{251,252} and dienes having the carbonyl *in the ring being formed* $(242 \rightarrow 243 + 244)$.^{251a} This difference was rationalized by a preference for the transition state that maximized overlap of the amide π -orbitals, and the diene π -orbitals. This secondary orbital interaction is analogous to the endo effect noted in sec. 11.4.C).



There are many synthetic examples carbocyclic, intramolecular Diels-Alder reactions that involve heteroatom substituents. In Martin and co-worker's synthesis of manzamine A,²⁵³ imine-diene **245** was heated to 150°C to give a 74% yield of **246**.



The concept of tethered intramolecular reactions has become popular. The basis of this concept is that the diene and alkene units are linked together by a species that allows an intramolecular Diels-Alder but can be chemically removed later. In the work of Batey and co-workers,^{254a} reaction of boronic acid (**247**) with sorbic alcohol (**248**) gave **249**, and heating in a sealed tube at 190°C in the presence of the radical inhibitor BHT (2,6-di-*tert*-butyl-4-phneylpheonol) gave the

- 252. Witiak, D.T.; Tomita, K.; Patch, R.J. J. Med. Chem. 1981, 24, 788.
- 253. Humphrey, J.M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A.K.; Martin, S.F. J. Am. Chem. Soc. 2002, 124, 8584.
- (a) Batey, R.A.; Thadani, A.N.; Lough, A.J. J. Am. Chem. Soc. 1999, 121, 450; (b) Boeckman, R.K., Jr.; Shao, P.; Wrobleski, S.T.; Boehmler, D.J.; Heintzelman, G.R.; Barbosa, A.J. J. Am. Chem. Soc. 2006, 128, 10572.

 ⁽a) Oppolzer, W.; Fröstl, W. Helv. Chim. Acta 1975, 58, 590; (b) Oppolzer, W.; Fröstl, W.; Weber, H.P. Ibid. 1975, 58, 593.

cycloadduct **250**. Oxidation with trimethylamine-*N*-oxide and hydrolysis gave a 90:10 mixture of **251/252** in 84% yield. The boronic ester linkage in **249** was a tether leading to the regio- and stereoselectivity of an intramolecular process. Treatment with the amine oxide and hydrolysis removed the tether to give the cycloadducts. In a synthesis of (+)-tetronolide by Boeckman and co-workers, an acetal tether was used to anchor an intramolecular Diels-Alder reaction.^{254b}



Silylalkyl tethers are also quite useful. In a synthesis of C-aryl glycosides by Martin and co-workers,²⁵⁵ treatment of aryl dichloride **253** with *tert*-butyllithium generated the benzyne intermediate. An intramolecular Diels-Alder reaction with the furan moiety led to **254** in 61% yield. Subsequent treatment with tetrabutylammonium fluoride and then trifluoroacetic acid cleaved the silane tether, generating an OH moiety, and opening the oxabicycloheptane unit to give **255** in 72% yield.



^{255.} Kaelin Jr., D.E.; Sparks, S.M.; Plake, H.R.; Martin, S.F. J. Am. Chem. Soc. 2003, 125, 12994.

11.9. ENANTIOSELECTIVE DIELS-ALDER REACTIONS

The diastereoselectivity inherent to the Diels-Alder reaction is apparent in several examples in preceding reactions. The reaction is not inherently enantioselective since there is no facial control (biasing approach of alkene to diene from a single face) for intermolecular reactions (some facial control is available for intramolecular reactions). The ortho rule, the endo rule (secondary orbital interactions) and steric interactions provide some orientational control, but facial control is also required for enantioselectivity. When ethyl acrylate reacts with 2-methyl-1,3-pentadiene, endo approach can occur from the bottom as in **256A**, or from the top as in **256B**. Clearly, the two products resulting from attack at opposite faces (**257A** and **257B**) are mirror images and enantiomers. This lack of facial selectivity leads to racemic mixtures in all Diels-Alder cyclizations discussed to this point.



As in Chapters 1-5 and 8-9, the key to enantioselectivity is providing both facial and orientational control in the transition state of the reaction. The orientational control (regioselection and endo selectivity) for the diene and alkene is provided by orbital interactions, including secondary orbital effects. As in previous chapters, facial selectivity will be provided by the presence of stereogenic centers in the molecule that usually make one face in the transition state more sterically hindered than the other. The diene can be constructed from a chiral precursor (a **chiral template**, sec. 10.9). Alternatively, a chiral auxiliary (X_c) can be attached to the diene or alkene. A third approach is related to using a chiral auxiliary in that a chiral material (usually a chiral catalyst) is added to the reaction, usually providing a transient chiral auxiliary (sec. 4.7.A). Catalytic, enantioselective Diels-Alder reactions are now well known, and many catalysts and auxiliaries are available.²⁵⁶ The rare earth (III) salt catalyzed asymmetric Diels-Alder reaction with a chiral dienophile in supercritical carbon dioxide has been reported, and

^{256.} Corey, E.J. Angew. Chem. Int. Ed. 2002, 41, 1651.

the use of alternative solvents is an on-going area of study.257

11.9.A Chiral Auxiliaries

A chiral auxiliary is a chiral molecule, usually derived from Nature, which is attached to the reaction substrate (in high yield and under mild conditions), and provides facial selectivity (and hopefully orientation control as well) in a reaction.²⁵⁸ After the reaction of interest, the auxiliary must be removed (in high yield and under mild conditions) to regenerate the original functional group. For a Diels-Alder reaction, the chiral auxiliary must be attached to either an achiral diene (as in 258) or an achiral dienophile (as in 261) to generate a chiral molecule. A limitation, of course, is the availability of a functional group in the alkene or diene that can react with a chiral auxiliary. A Diels-Alder reaction with 258, for example, would generate 259 as a mixture of diastereomers, each in high enantiomeric purity (% ee, sec. 1.4.F). The auxiliary is then removed to give the chiral target 260. A similar sequence with 261 generated 262, and removal of X_c gave 263. The auxiliary provides facial selectivity in the Diels-Alder reaction, transferring that chirality to the cycloadduct. The Diels-Alder reactions of both **258** and **261** may proceed with excellent enantioselectivity, but may proceed with moderate diastereoselectivity. This problem of diastereoselectivity and enantioselectivity must be addressed in all asymmetric reactions, and was seen in reductions (Chap. 4) as well as nucleophilic carbon bond forming reactions (Chap. 8), and especially in enolate reactions (Chap. 9).



Morrison and Mosher²⁵⁹ showed that menthyl was an early auxiliary, and when an acrylic acid derivative reacts with menthol to form a menthyl ester, **264**, asymmetric induction is possible upon reaction with cyclopentadiene to give diastereomers **265** and **266**,²⁶⁰ as shown in Table 11.7.²⁵⁹ In the absence of a Lewis acid, however, the % ee is rather poor.

^{257.} Fukuzawa, S.; Metoki, K.; Esumi, S. Tetrahedron 2003, 59, 10445.

^{258.} For a review of bicyclic lactam chiral auxiliaries, see Groaning, M.D.; Meyers, A.I. Tetrahedron 2000, 56, 9843.

^{259.} Morrison, J.D.; Mosher, H.S. Asymmetric Organic Reactions, Amer. Chem. Soc., Washington, D.C., 1976, p256.

^{260. (}a) Sauer, J.; Kredel, J. *Tetrahedron Lett.* **1966**, 6359; (b) Farmer, R.F.; Hamer, J. J. Org. Chem. **1966**, 31, 2418; (c) Cervinka, O; Kríz, O. Collect. Czech. Chem. Commun. **1968**, 33, 2342.

/ ← Me ►		$= \longrightarrow \frac{1. \text{ LiAlH}_4}{2. \text{ H}_2\text{O}}$	10 265 + 1	HO 266
<u>Catalyst</u>	<u>Solvent</u>	<u>Temperature (°C)</u>	<u>265 [%ee]</u>	<u>266 [%ee]</u>
None	CH_2Cl_2	0	(+) [9]	
None		35	(+) [7]	(+) [3.1]
AlCl ₃ •OEt ₂		0	(+) [49]	(-) [36]
-		-70	(+) [67]	
BF ₃ •OEt ₂		0	(+) [74]	(-) [43]
5 -		-20	(+) [82-85]	
SNCl ₄	PhMe	48	(+) [41]	
None	Neat	160	(+) [6]	
[Reprinted by courtes <i>Reactions</i> , American	y of Professor Jame Chemical Society,	es D. Morrison from Morrison, J. Washington, DC 1976 , pp. 256.]	D.; Mosher, H.S. Asym	metric Organic

 Table 11.7.
 Selectivity in the Diels-Alder Reaction of Cyclopentadiene and Menthyl Acrylate

One of the first examples of an asymmetric Diels-Alder reaction is the work of Walborsky et al.²⁶¹ in the reaction of (–)-dimenthyl fumarate (**267**) and 1,3-butadiene to give **268** and **269**, after reduction of the ester products with lithium aluminum hydride.²⁶² Reaction in toluene using a Lewis acid catalyst generally provided the best asymmetric induction, in good yield. Hydride reduction of esters (sec. 4.2.B) is a common method for removing ester auxiliaries. In general, menthol type auxiliaries provide only moderate selectivity.²⁶³



In Oppolzer's review,²⁶⁴ several chiral auxiliaries related to menthol and other chiral alcohols were presented, giving the diastereomeric endo adducts **270** and **271**, as shown in Table 11.8.²⁶⁵ In all cases, the chiral ester in Table 11.8 provided good-to-excellent selectivity. Oppolzer discussed the source of this selectivity by invoking Figure 11.13²⁶⁵ (from 5-benzyloxymethyl cyclopentadiene) in which the derivatized menthyloxy chiral auxiliary **272** provided facial selectivity to the acrylate, for attack from either the *re* face or the *si* face. The *si* face is less

^{261.} Walborsky, H.M.; Barash, L.; Davis, T.C. Tetrahedron 1963, 19, 2333.

^{262.} Reference 200, p 253.

^{263.} Roush, W.R.; Gillis, H.R.; Ko, A.I. J. Am. Chem. Soc. 1982, 104, 2269.

^{264.} Oppolzer, W. Angew. Chem. Int. Ed. 1984, 23, 876.

^{265.} Oppolzer, W.; Kurth, M.; Reichlin, D.; Chapuis, C.; Mohnhaupt, A.; Moffatt, F. Helv. Chim. Acta 1981, 64, 2802.

hindered and 273 [the (*R*) cycloadduct] is preferred to 274, consistent with the results in Table 11.8. Figure 11.13 can be used to illustrate the source of facial selectivity for other chiral auxiliaries. The poor-to-moderate asymmetric induction with menthol and related auxiliaries contrasts with Trost's use of 276 with napthoquinone 275, which gave 98% of 277 with >97% ee.²⁶⁶





Other auxiliaries can be attached to either the dienophile or the diene. In Rawal and Kozmin's synthesis of (-)- α -elemene, a chiral pyrrolidine unit attached to the diene unit of **70** and served as a chiral auxiliary (see sec. 11.4.C.iii). In that synthesis, the Diels-Alder adduct was **71**, but the auxiliary was removed by elimination to an alkene unit later in the synthesis.¹⁰⁰

266. Trost, B.M.; O'Krongly, D.; Belletire, J.L. J. Am. Chem. Soc. 1980, 102, 7595.



Figure 11.13. Facial selectivity of chiral acrylates in the Diels-Alder reaction. [Reproduced with permission from Oppolzer, W. *Angew. Chem. Int. Ed. 1984, 23,* 876. Copyright © 1984 VCH Weinheim.]



Evans developed a new generation of chiral auxiliaries, based on conversion of amino alcohols to oxazolidinone derivatives. The use of these auxiliaries to give the corresponding conjugated amide **278** led to excellent selectivity in the intramolecular Diels-Alder reaction, which generated mixtures of **279** and **280**.²⁶⁷ Coordination with the Lewis acid catalyst generated a complex in which facial selectivity is enhanced relative to the uncomplexed species. When dimethylaluminum chloride was used as a Lewis acid catalyst with **281**, for example, chelated intermediate **282** was formed. This provided orientational control for the dienophile, and the chiral nature of the auxiliary provided the requisite facial control, with approach of the diene from the less sterically hindered face. Good selectivity was observed with the intermolecular Diels-Alder reaction as well.²⁶⁸ In a synthesis of (+)-eutipoxide B by Okamura and co-

^{267.} Evans, D.A.; Chapman, K.T.; Bisaha, J. Tetrahedron Lett. 1984, 25, 4071.

^{268.} Evans, D.A. Chapman, K.T.; Bisaha, J. J. Am. Chem. Soc. 1984, 106, 4261.

workers,²⁶⁹ the Cinchonine-catalyzed reaction of pyrone **283** and acrylamide **284** (containing the **Evan's auxiliary** shown) proceeding good yield, with greater than 95% selectivity for **285**.



Oppolzer et al. developed a different set of auxiliaries based on a camphor precursor,²⁷⁰ typified by sultam **286** (**Oppolzer's sultam**) and used in a chiral synthesis of the aglycone of loganin.²⁷¹ Sultam **286** was also the precursor to acrylamide **287**, which reacted with diene **288** to give a 66% yield of **289** (7:1 *exo:endo*), in Roush and co-worker's synthesis of the spirotetronate subunits of quartromicin.²⁷² Selectivity in this Diels-Alder reaction is due to chelation of the sultam unit with the catalyst (MeAlCl₂).



Many auxiliaries give excellent asymmetric induction in the Diels-Alder reaction. Helmchen and Schmierer developed an auxiliary based on camphor that is quite useful.²⁷³ Helmchen²⁷⁴ also prepared the lactone auxiliary **290** and the imide auxiliary **292**, and showed they give

^{269.} Shimizu, H.; Okamura, H.; Iwagawa, T.; Nakatani, M. Tetrahedron 2001, 57, 1903.

^{270.} Oppolzer, W.; Chapuis, C.; Dupuis, D.; Guo, M. Helv. Chim. Acta 1985, 68, 2100.

^{271.} Vandewalle, M.; van der Eycken, J.; Oppolzer, W.; Vullioud, C. Tetrahedron 1986, 42, 4035.

^{272.} Roush, W.R.; Limberakis, C.; Kunz, R.K.; Barda, D.A. Org. Lett. 2002, 4, 1543.

 ⁽a) Helmchen, G.; Schmierer, R. Angew. Chem. Int. Ed. 1981, 20, 205; (b) Schmierer, R.; Grotemeier, G. Helmchen, G.; Selim, A. Ibid. 1981, 20, 207.

^{274.} Poll, T.; Abdel Hady, A.F.; Karge, R.; Linz, G.; Weetman, J.; Helmchen, G. Tetrahedron Lett. 1989, 30, 5595.

opposite enantioface selectivity in the Diels-Alder reaction. In the presence of a Lewis acid such as TiCl₄, differences in coordination site led to a different chiral face in the transition state of the cycloaddition and opposite stereochemistry. Helmchen used an auxiliary based on **290** in a synthesis of cyclosarkomycin.²⁷⁵ Other auxiliaries include **291**, developed by Marchand-Brynaert²⁷⁶ and co-workers for 1-amino dienes, and the *exo*-selective auxiliary **293** developed by Kudo and Kawamura,²⁷⁷



Ghosez and co-workers showed that changing the catalyst in Diels-Alder reactions using a chiral auxiliary can influence selectivity. When **294** reacted with diene **295**, in the presence of a silyl triflate catalyst, an 88:12 mixture of **296/297** was obtained in 96%.²⁷⁸ Changing the catalyst to europium [Eu(fod)₃], however, gave 98% of **297** (0:100 **296/297**). A variety of auxiliaries have been developed that can be very effective in catalyzing Diels-Alder reactions with high asymmetric induction. It is clear that the best results are obtained when the substrate-auxiliary complex can chelate to the catalyst. A major drawback with these auxiliaries is that they can sometimes be difficult to remove (vigorous aqueous acid or base or treatment with LiAlH₄ may be required). Dienes and dienophiles must have heteroatom substituents for these auxiliaries or other methodology must be developed.



11.9.B. Chiral Additives and Chiral Catalysts

Clearly related to chiral auxiliaries are chiral additives, which usually form transient auxiliaries to provide the requisite facial selectivity. In Section 4.7.A, we saw that naturally occurring chiral amines were added to reducing agents to achieve asymmetric induction. Protected proline and abrine esters (*L*-abrine is *N*-Methyl-*L*-tryptophan) and related compounds have

^{275.} Linz, G.; Weetman, J.; Abdel Hady, A.F.; Helmchen, G. Tetrahedron Lett. 1989, 30, 5599.

^{276.} Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. J. Org. Chem. 2003, 68, 9809.

^{277.} Kawamura, M.; Kudo, K. Chirality 2002, 14, 727.

^{278. (}a) Lamy-Schelkens, H.; Ghosez, L. *Tetrahedron Lett.* 1989, 30, 5891; (b) Lamy-Schelkens, H.; Giomi, D.; Ghosez, L. *Ibid.* 1989, 30, 5887.

been used as chiral catalysts.²⁷⁹ These amines can also be used in Diels-Alder reactions, with

variable results. One example is the reaction of **298** with *N*-methylmaleimide to give **299**, ²⁸⁰ in the presence of a chiral additive. The use of various chiral amine additives [quinine, quinidine, cinchonine, cinchonidine, (*S*)-prolinol, and (*1R*,*2S*)-



N-methylephedrine], gave enantiomeric excesses between 16-61%) in the cycloadduct. In this particular example, quinidine proved the most effective additive with a 61% ee. Presumably, coordination between the chiral amine and **298** via hydrogen-bonding (or a dipole-dipole interaction) provides diastereoselection in the subsequent reaction with *N*-methylmaleimide.

Preparation of a chiral catalyst will provide facial selectivity when it coordinates to the substrate (usually the dienophile), forming a chiral transition state containing the transient auxiliary. Roush and co-workers used menthoxyl and bornyloxyaluminum catalysts,²⁶³ providing an example in which traditional chiral materials are attached to aluminum chloride. Significantly more effective catalysts have been developed based on coordination of chiral molecules [usually bis(amines) or diols] with aluminum or titanium reagents. Corey et al. prepared chiral catalyst **301**, which reacted with **300** to form chiral complex **302**.²⁸¹ This complex was formed *in situ*, and reacted with cyclopentadiene to give an 88% yield of **303**, with 94% ee (in a ratio of 96:4 endo/exo).



Corey and co-workers developed other catalysts for enantioselective Diels-Alder reactions. One is a C_2 -symmetric chiral bis(oxazoline)-Fe(III) complex (**304**).²⁸² Similar copper-coordinated catalysts have been developed and give good-to-excellent enantioselectivity in Diels-Alder reactions.²⁸³ Analogs of **300** reacted with cyclopentadiene in the presence of a **304**•FeCl₂I

^{279.} Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C. J. Am. Chem. Soc. 2000, 122, 4243.

^{280.} Riant, O.; Kagan, H.B. Tetrahedron Lett. 1989, 30, 7403.

^{281.} Corey, E.J.; Imwinkelried, R.; Pikul, S.; Xiang, Y.B. J. Am. Chem. Soc. 1989, 111, 5493.

^{282.} Corey, E.J.; Imai, N.; Zhang, H.-Y. J. Am. Chem. Soc. 1991, 113, 728.

^{283.} For copper coordinated catalysts, see (a) Evans, D.A.; Barnes, D.M.; Johnson, J.S.; Lectka, T.; von Matt, P.; Miller, S.J.; Murry, J.A.; Norcross, R.D.; Shaughnessy, E.A.; Campos, K.R. J. Am. Chem. Soc. 1999, 121, 7582. For copper and zinc coordinated catalysts see (b) Yao, S.; Roberson, M.; Reichel, F.; Hazell, R.G.; Jørgensen, K.A. J. Org. Chem. 1999, 64, 6677.

catalyst to give cycloadducts with good enantioselectivity (93:7, with 99:1 endo/exo-selectivity) at -50° C in dichloromethane (15, 10 mol% of the catalyst).²⁸² The FeI₃ complex that is shown with **304**, as well as the FeCl₃ complex gave slightly poorer selectivity than the FeCl₂I complex. The (*S*)-tryptophan derived oxazoborolidine (**305**) catalyst was designed to facilitate intramolecular interactions in highly enantioselective Diels-Alder reactions.²⁸⁴ Oxazolidinone catalyst **68**, as the hexafluoroantimonate complex, in Sect. 11.4.C.ii, is another example of an extremely useful catalyst for the Diels-Alder reaction related to **304**. In a synthesis of estrone,²⁸⁵ Corey and co-workers reacted **307** with **308**, in the presence of chiral catalyst **306** (an oxazaborolidinium salt), to give a 92% yield of **309**, in 94% ee. Catalysts related to **306** have been shown to be broad spectrum catalysts for enantioselective Diels-Alder reactions.²⁸⁶



Yamamoto and co-workers reported an asymmetric hetero-Diels-Alder reaction that was catalyzed by a chiral organoaluminum reagent (311).²⁸⁷ When diene **310** reacted with benzaldehyde in the presence of 10 mol% of **311**, a mixture of *cis*-dihydropyrone (**312**) and *trans-d*ihydropyrone (**313**) was obtained in 77 and 7% yield, respectively. The optical activity of **312** was 95% ee, and that of **313** was 53% ee.²⁸⁷ In the complex that mediates this reaction, the diene approaches benzaldehyde with an endo alignment that minimizes steric repulsion between the incoming diene and the triphenylsilyl moiety on that face.



^{284.} Corey, E.J.; Loh, T.-P. J. Am. Chem. Soc. 1991, 113, 8966.

- 285. Hu, Q.-Y.; Rege, P.D.; Corey, E.J. J. Am. Chem. Soc. 2004, 126, 5984.
- 286. Ryu, D.H.; Lee, T.W.; Corey, E.J. J. Am. Chem. Soc. 2002, 124, 9992.
- 287. Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. J. Am. Chem. Soc. 1988, 110, 310.

Narasaka et al. developed a titanium catalyst generated by complexation with chiral diols.²⁸⁸ The dienophile must contain functionality that will coordinate with the metal catalyst to form a chiral complex, and these catalysts are less effective with dienes and dienophiles that do not contain heteroatoms. A related titanium-BINOL complex has been used to catalyze Diels-Alder reactions.²⁸⁹ Kelly prepared a transient boron catalyst, prepared *in situ* with borane and a chiral diol.²⁹⁰ It is clear that chiral additives, particularly chiral catalysts can be effective. The asymmetric induction is usually good to excellent with properly designed dienophiles. Effective chiral catalysts continue to be reported and will undoubtedly be a major force in chiral synthesis involving Diels-Alder reactions.

11.9.C. Chiral Templates

The last approach to chiral synthesis begins with a chiral precursor whose components will be integrated into the final product, which is the **chiral template approach** (sec. 10.9). The examples of asymmetric syntheses involving Diels-Alder **templates** are as varied as the



targets. One is by Oppolzer, who reported an asymmetric synthesis of pumiliotoxin C via Diels-Alder cyclization of **314**, prepared from (*R*)-norvaline, to give **315**.²⁹¹

Carbohydrates are efficient chiral templates and have been used in the Diels-Alder reaction. Sherburn and Lilly used L-ascorbic acid as a template to synthesize **316**.²⁹² Heating this compound in refluxing toluene led to a 96:4 mixture of **317** and **318** (68% yield). The chirality inherent in the carbohydrate precursor provides the needed facial selectivity that is transferred to the cycloadduct product. The use of chiral templates for preparing Diels-Alder precursors will undoubtedly increase in importance. As the need for enantiomerically pure material increases, the chiral template driven Diels-Alder reactions will be increasingly effective.



 ⁽a) Narasaka, K.; Iwasawa, N.; Inoue, M.; Yamada, T.; Nakashima, M.; Sugimori, J. J. Am. Chem. Soc. 1989, 111, 5340; (b) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N. Chem. Lett. 1987, 2409.
 Mikami, K.; Motoyama, Y.; Terada, M. J. Am. Chem. Soc. 1994, 116, 2812.

Composizer, W., Plaskamp, E. Helv. Chim. Acta 1977, 60, 20 Lilly, M.J.; Sherburn, M.S. Chem. Commun. 1997, 967.

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Kelly, T.R.; Whiting, A.; Chandrakumar, N.S. J. Am. Chem. Soc. 1994, 110, 2812.

^{290.} Keny, I.K., Winning, A., Chandrakumar, N.S. J. Am. Chem. Soc. 19 291. Oppolzer, W.; Flaskamp, E. *Helv. Chim. Acta* 1977, 60, 204.

11.10. [2+2]-CYCLOADDITION REACTIONS

The Diels-Alder reaction occupies a prominent place in organic synthesis, but other pericyclic reactions are quite useful. One is the [2+2]-cycloaddition that occurs between two alkenes, or between an alkene and a carbonyl or imine.²⁹³ Cyclobutanes and oxetanes are prepared by this reaction, and β -lactams and β -lactones have been prepared. This section will focus on both thermal and photochemical [2+2]-cycloaddition reactions.

11.10.A. Thermal [2+2]-Cycloadditions

In Section 11.3, thermal [2+2]-cycloaddition reactions that form cyclobutane derivatives such as **321**^{294,10a} were shown to be symmetry forbidden, but photochemically allowed. There are, however, several examples of thermal [2+2]-cycloadditions that probably occur by a radical or dipolar intermediate (319 or 320, respectively), or by HOMO-HOMO or LUMO-LUMO interactions.²⁹⁵ Lewis-acid catalyzed reactions of alkynes with alkenes or conjugated carbonyl compounds are also known,²⁹⁶ proceeding via a metal-stabilized cationic intermediate.^{296b} Reaction of dimethylaminoisobutene (322) with methyl acrylate gives cyclobutane 324 by what is believed to be a zwitterionic intermediate (323).²⁹⁷ As seen in the reaction of 322, enamines are partners and alkynes react with ketenes to form cyclobutene derivatives.²⁹⁸ Ionic intermediates need not be invoked in all cases, since some reactions proceed via diradical intermediates. The HOMO of 322 and LUMO of methyl acrylate can be used to predict the regiochemistry in **324**.²⁹⁹ In general, the presence of an electron-withdrawing group on a ketene. such as a chlorine, an alkoxy group, an aryl group or a vinyl group greatly enhances the rate of the [2+2]-cycloaddition reaction with alkenes, particularly intramolecular cycloadditions.³⁰⁰ It is also known that cis alkenes are more reactive than trans alkenes in reactions with ketenes.³⁰¹ Cycloaddition reactions with cis alkenes are stereospecific, but some loss of stereochemistry is observed in reactions with trans alkenes.^{299,300,43}

^{293. (}a) Reference 65, pp 161-165; (b) Lee-Ruff, E.; Mladenova, G. Chem. Rev. 2003, 103, 1449.

^{294.} Reference 80b, pp 33-63.

^{295.} Reference 80b, p 35.

⁽a) Dopper, J. H.; Greijdanus, B.; Oudman, D.; Wynberg, H. J. Chem. Soc. Chem. Commun. 1975, 972; (b) Meyers, A. I.; Tschantz, M. A.; Brengel, G. P. J. Org. Chem. 1995, 60, 4359; (c) Groaning, M. D.; Brengel, G. P.; Meyers, A. I. Tetrahedron 2001, 57, 2635.

^{297.} Brannock, K.C.; Bell, A.; Burpitt, E.D.; Kelly, C.A. J. Org. Chem. 1961, 26, 625.

^{298.} For a synthetic example, see Fex, T.; Froborg, J.; Magnusson, G.; Thorén, S. J. Org. Chem. 1976, 41, 3518.

^{299.} Reference 80b, p 33.

^{300. (}a) Snider, B.B. Chem. Rev. 1988, 88, 793; (b) Snider, B.B.; Walner, M. Tetrahedron 1989, 45, 3171.

^{301. (}a) Ghosez, L.; O'Donnell, M.J. in *Pericyclic Reactions, Vol. II*, Marchand, A.P.; Lehr, R.E. (Eds), Academic Press, New York, 1977, pp 79-140; (b) Frey, H.M.; Isaacs, N.S. J. Chem. Soc. B 1970, 830.



Ketenes ($R_2C=C=O$) react at the C=C unit via thermal [2+2]-cycloaddition reactions to give cyclobutanone derivatives. Ketenes are highly electrophilic due to a low-lying LUMO (π^* C=O, and the HOMO is relatively high in energy (see Table 11.1). Ketene itself has a HOMO of -12.55 eV and a LUMO of +2.55 eV, 43,302 and those values along with those of the orbital coefficients are shown in Figure 11.14 (also see Table 11.1). Polarization of the C=C unit in ketene (the combination of electrophilic and nucleophilic character) is responsible for the facile [2+2]-cycloaddition reactions. As mentioned above, the presence of an electronwithdrawing group enhances the rate of the [2+2]-cycloaddition reaction. Inspection of Table 11.1 shows that the HOMO for ketene is -12.55 eV, but the HOMO for PhCH=C=O is -10.61eV, that for ClCH=C=O is -9.24 eV and that for Cl₂C=C=O is -9.15 eV. Clearly, the presence of these groups raises the energy of the HOMO, and would be expected to increase the rate of a cycloaddition driven by the LUMO of an alkene. This effect has been noted in many intermolecular reactions of ketenes and alkenes.³⁰³ The attempted intramolecular cyclization (see below) of 325 (X = H) failed. When the α -chloro analog (325, X = Cl) was prepared, however, treatment with triethylamine led to **326**, which cyclized to give a 55% yield of the [2+2]-cycloadduct (327) along with 19% of the ene adduct (328, see sec. 11.13) where X = Cl.



Figure 11.14. Orbital Diagram for Ketene.

^{302. (}a) Reference 7, p 143; (b) Reference 80b, p 33-42.

^{303. (}a) Krepski, L.R.; Hassner, A. J. Org. Chem. 1978, 43, 2879; (b) Bak, D.A.; Brady, W.T. Ibid. 1979, 44, 107;
(c) Martin, P.; Greuter, H.; Bellus, D. Helv. Chim. Acta. 1984, 64, 64; (d) Brady, W.T. Synthesis 1971, 415.



In a typical reaction, dimethylketene (**329**) and ethene were heated to give cyclobutanone **330** in a reaction controlled by the HOMO_{alkene}-LUMO_{ketene} interaction.³⁰⁴ Inspection of the orbital picture for this reaction (see **331**) shows that [2+2]-cycloadditions are allowed when one component is suprafacial and the other is antarafacial. In **331**, the HOMO of the alkene is of the correct symmetry to interact with the low-lying LUMO of the ketene.^{305a} Reaction of an alkene and a ketene (see **331**) yields a cyclobutanone (**332**).³⁰⁶ Ketenes such as **329** are readily generated by reaction of an acid chloride with an amine,³⁰⁶ or by treatment with Zn-Cu in the case of α -chloro acid chlorides. Since carboxylic acids and acid chlorides are readily available, ketenes are convenient partners for reaction with both alkenes and dienes.³⁰⁷ In Delair and co-worker's synthesis of (+)-amphorogynine A,³⁰⁸ the acid chloride of trichloroacetic acid was treated with Zn-Cu in the presence of POCl₃ to give dichloroketene (**333**), which reacted with **334** to give dichlorocyclobutanone **335** in >90%% yield.



[Reprinted with permission from Tidwell, T.T. *Ketenes*, Wiley, New York, **1995**, p 487. Copyright © **1995** by John Wiley and Sons, Inc.]



The intramolecular version of this reaction is usually more efficient than the intermolecular version. When **336** (R = Me) was treated with triethylamine (0.2% solution of acid chloride in refluxing dichloromethane), ketene **337** (R = Me) was formed and an intramolecular

^{304. (}a) Reference 80b, pp 38-40; (b) Sustmann, R.; Ansmann, A.; Vahrenholt, F. J. Am. Chem. Soc. 1972, 94, 8099.

^{305. (}a) Tidwell, T.T. Ketenes, Wiley, New York, 1995, p 487; (b) Also see Reference 80b, p 39.

^{306.} Brady, W.T. Tetrahedron 1981, 37, 2949.

^{307.} For a reaction with cyclopentadiene, see Grieco, P.A. J. Org. Chem. 1972, 37, 2363.

Roche, C.; Kadlecčiková, K.; Veyron, A.; Delair, P.; Philouze, C.; Greene, A. E.; Flot, D.; Burghammer, M. J. Org. Chem. 2005, 70, 8352.

[2+2]-cycloaddition gave an 80% yield of **338**.³⁰⁹ Ghosez reported, however, that reaction of **336** (R = H) under the same conditions gave only 3% of **338** (R = H). Many unactivated ketones (see above) show similar poor reactivity, and to enhance the reactivity of such molecules Ghosez and co-workers developed a ketene iminium salt³¹⁰ cyclization procedure. Pyrrolidine amide **339** was treated with triflic anhydride $[(CF_3SO_2)_2O]$ and collidine to generate the ketene iminium salt (**340**). Subsequent internal [2+2]-cycloaddition gave **341**, and after hydrolysis of the iminium salt product **338** was obtained in 75% yield. Ghosez and Marchand-Brynaert showed that ketene iminium salts were more electrophilic than ketenes and did not dimerize.³¹¹



Another example of this approach is the conversion of **342** to **343** in ~ 65% yield,.³¹² There are many examples of internal [2+2]-cycloaddition of **344** to **345**),³¹³ and Brady and Giang.³¹⁴ In



involving vinyl ketenes, Snider defined three different reaction types: Type I (the ketene carbon has a side chain),³¹⁵ Type II (a side chain is attached α - to the ketene carbon),³¹⁶ and Type III (a side chain is attached β - to the ketene

both Snider's and Brady's examples, the presence of an α -alkoxy substituent led to a more facile cycloaddition. As mentioned above, vinyl ketenes also react well in the cycloaddition. For intramolecular [2+2]-cycloadditions



- 309. Markó, I.; Ronsmans, B.; Hesbain-Frisque, A.-M.; Dumas, S.; Ghosez, L.J. Am. Chem. Soc. 1985, 107, 2192.
- 310. Falmagne, J.B.; Escudero, J.; Taleb-Sahraoui, S.; Ghosez, L. Angew. Chem. Int. Ed. 1981, 20, 879.
- Ghosez, L.; Marchand-Brynaert, J. Iminium Salts in Organic Chemistry, Part I, Böhme, J.; Viehe, H.G. (Eds), Wiley, New York, 1976, pp 421-532.
- 312. Monache, G.D.; Misiti, D.; Salvatore, P.; Zappia, G.; Pierini, M. Tetrahedron: Asymmetry 2000, 11, 2653.
- 313. (a) Snider, B.B.; Hui, R.A.H.F.; Kulkarni, Y.S. J. Am. Chem. Soc. 1985, 107, 2194; (b) Snider, B.B.; Hui, R.A.H.F. J. Org. Chem. 1985, 50, 5167.
- 314. Brady, W.T.; Giang, Y.F. J. Org. Chem. 1985, 50, 5177.
- 315. Kulkarni, Y.S.; Burbaum, B.W.; Snider, B.B. Tetrahedron Lett. 1985, 26, 5619.
- 316. Kulkarni, Y.S.; Snider, B.B. J. Org. Chem. 1985, 50, 2809

carbon).^{313a} In reactions of ketenes, primarily from the work of Ghosez and co-workers,³⁰⁹ Snider et al. (as in the conversion example of a Type I cyclization is the conversion of acid **346** to the ketene (**347**) and cyclization to **348** in 97% yield.³¹⁷ With vinyl ketenes, [1,5]-sigmatropic hydrogen shifts are sometimes a problem³¹⁷ (sec. 11.12.A). Snider used a Type III cyclization of this type in a synthesis of isocomene.³¹⁸ Funk et al. synthesized clovene using this methodology,³¹⁹ and Ernst and co-workers showed this methodology, Halcomb and co-worker reported an intramolecular ketene-allene cycloaddition.³²¹



Ketenes react with imines via [2+2]-cycloaddition to produce β -lactams.³²² An example is the reaction of the acid chloride of phenylacetic acid with Proton SpongeTM [1,8-bis(dimethylamino) naphthalene] to give ketene **349**, which reacted with the tosyl imine shown and a quinuclidine catalyst to give a 65% yield of β -lactam **350** in 96% ee.³²³ Chiral ammonium salts derived from chiral quinidine compounds and Cinchona alkaloids have been used to catalyze the [2+2] cycloaddition of ketenes and imines, producing β -lactams with excellent enantioselectivity.³²⁴ Ketenes are useful in many asymmetric syntheses.³²⁵ *N*-Substituted isocyanates also undergo thermal [2+2]-cycloaddition reactions with alkenes, generating β -lactams.³²⁶ Aldehydes react with silylketenes to give β -lactones, as in the conversion of **351** to **352**.³²⁷



^{317.} Lee, S.Y.; Kulkarni, Y.S.; Burbaum, B.W.; Johnston, M.I.; Snider, B.B. J. Org. Chem. 1988, 53, 1848.

^{318.} Snider, B.B.; Beal, R.B. J. Org. Chem. 1988, 53, 4508.

^{319.} Funk, R.L.; Novak, P.M.; Abelman, M.M. Tetrahedron Lett. 1988, 29, 1493.

^{320.} Veenstra, S.J.; De Mesmaeker, A.; Ernst, B. Tetrahedron Lett. 1988, 29, 2303.

^{321.} McCaleb, K.L.; Halcomb, R.L. Org. Lett. 2000, 2, 2631.

^{322.} For reviews of the formation of β-lactams, see (a) Brown, M.J. *Heterocycles* 1989, 29, 2225; (b) Isaacs, N.S. *Chem. Soc. Rev.* 1976, 5, 181; (c) Mukerjee, A.K.; Srivastava, R.C. *Synthesis* 1973, 327. For a review of cycloaddition reactions of imines, see (d) Sandhu, J.S.; Sain, B. *Heterocycles* 1987, 26, 777.

^{323.} Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Drury III, W.J.; Lectka, T. J. Am. Chem. Soc. 2000, 122, 7831.

^{324.} Taggi, A.E.; Hafez, A.M.; Wack, H.; Young, B.; Ferraris, D.; Lecktka, T. J. Am. Chem. Soc. 2002, 124, 6626.

^{325.} Orr, R.K.; Calter, M.A. Tetrahedron 2003, 59, 3545.

^{326. (}a) Johnston, D.B.R.; Schmitt, S.M.; Bouffard, A.F.; Christensen, B.G. J. Am. Chem. Soc. 1978, 100, 313;
(b) Bouffard, A.F.; Johnston, D.B.R.; Christensen, B.G. J. Org. Chem. 1980, 45, 1130.

^{327.} Fournier, L.; Kocienski, P.; Pons, J.-M. Tetrahedron 2004, 60, 1659.



Thermal [2+2]-cycloadditions lead to the following disconnections:



The intramolecular ketene-alkene cycloaddition has also been used to prepare highly substituted phenols. As originally formulated, a cyclobutenone such as **353** was converted to a phenol derivative (**357**). When **353** was heated in benzene, ketene **354** was formed. When done in the presence of an alkyne,³²⁸ an *in situ* [2+2]-cycloaddition led to a new cyclobutenone (**355**), but a four-electron electrocyclic cleavage reaction occurred under the reaction conditions to give **356**. This compound also reacted, via a six-electron electrocyclic ring closure to form a six-membered ring, and tautomerization gave the aromatic final product, phenol **357**.



This sequence is now known as the **Danheiser annulation**.³²⁹ Electrocyclic reactions such as this are discussed in section 11.11. In a synthetic application taken from Danheiser and co-worker's synthesis of (–)-ascochlorin, alkyne **358** was photolyzed in the presence of **359**,

^{328. (}a) Danheiser, R.L.; Gee, S.K. J. Org. Chem. 1984, 49, 1672; (b) Danheiser, R.L.; Brisbois, R.G.; Kowalczyk, J.J.; Miller, R.F. J. Am. Chem. Soc. 1990, 112, 3093.

^{329.} Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, *2005*, pp. 196-197

and then refluxed in toluene to give **360** in 65% yield.³³⁰ Resorcinols³³¹ have been prepared by this method. Liebeskind and co-workers reported a related method for the synthesis of highly substituted quinones.³³²



11.10.B. General Principles of Photochemistry

It is known that a normal [2+2]-cycloaddition of two alkene moieties does not occur readily under thermal reaction conditions. In one sense, therefore, the thermal [2+2]-cycloaddition reactions noted in Section 11.10.A can be considered highly useful special cases. In contrast to the thermal reaction, photochemically induced cycloaddition occurs with great ease. In the photochemical [2+2]-cycloaddition, promotion of an electron from the populated HOMO of the alkene to the unpopulated LUMO to generate an excited state. Fleming's generic orbital pictures³³³ can be used in a simple illustration of this process. The HOMO and LUMO for substituted alkenes is shown in Figure 11.2. For a reaction to occur between two alkenes, the HOMO of one alkene must react with the LUMO of the second, but the HOMO_{alkene}-LUMO_{alkene} interaction is promoted from the filled HOMO to the empty LUMO. The higher energy orbital is now a **singly occupied molecular orbital** (a **SOMO**, see section 2.4.B), and is of the correct symmetry to interact with the LUMO of another alkene. In other words, reaction occurs by the LUMO*_{alkene} interaction, which is now symmetry allowed (where * represents the excited state).

Before discussing photochemical reactions, some general principles of photochemistry will be introduced. Photochemistry is "concerned with the chemical change that may be brought about by the absorption of light".³³⁴ Chemical change is not a requirement, however, since **fluorescence** (light emitted from a species that has absorbed radiation) and **chemiluminescence** (light emitted as a product of a chemical reaction) can occur.³³⁴ A molecule can absorb a photon of light, and the photoactivated species can undergo [2+2]-cycloaddition or a variety of other reactions (sec. 13.4).

^{330.} Dudley, G.B.; Takaki, K.S.; Cha, D.D.; Danheiser, R.L. Org. Lett. 2000, 2, 3407.

^{331.} Danheiser, R.L.; Nishida, A.; Savariar, S.; Trova, M.P. Tetrahedron Lett. 1988, 29, 4917.

^{332.} Liebeskind, L.S.; Iyer, S.; Jewell, Jr., C.F. J. Org. Chem. 1986, 51, 3065.

^{333.} Reference 7, pp 128, 219.

^{334.} Wayne, R.P. Principles and Applications of Photochemistry, Oxford Univ. Press, Oxford, 1988, p 1.

Application of light increases the energy of a molecule according to

$$E = h v$$
 where $v = \frac{c}{\lambda}$ 11.5

where *h* is Planck's constant (6.63x10⁻³⁴ J sec), *c* is the speed of light (3x10⁸ m sec⁻¹), v is its frequency in sec⁻¹, and λ is the wavelength of the light in nm, which is inversely proportional to frequency. As *E* is usually expressed in kcal mol⁻¹, the molecular value of *E* calculated from Eqn 11.5 must be multiplied by Avogadro's number, $N = 6.02 \times 10^{23} \text{ mol}^{-1}$. This expression gives $E = 2.86 \times 10^4 / \lambda_{nm}$ kcal mol⁻¹, including conversion factors. An energy of 1 kcal mol⁻¹ corresponds to a wavelength (λ) of 2.86 x 10⁵ Å, and in general:³³⁵

1 kcal mol⁻¹ =
$$\frac{2.86 \times 10^5 \text{ kcal mol}^{-1}}{\lambda \text{ [Å]}}$$
 and $\lambda = 2.86 \times 10^5 \text{ Å}$ 11.6

This wavelength corresponds to a wavenumber (v) given by

$$v = \frac{c}{\lambda} = \frac{10_8 \text{ Å cm}^{-1}}{2.86 \text{x} 10^5 \text{ Å}} = 353 \text{ cm}^{-1}, \text{ also} = 1 \text{ kcal mol}^{-1}$$
 11.7

Therefore, 1 kcal mol⁻¹ = 2.86×10^5 Å = 353 cm⁻¹, which is in the infrared (IR) region of the electromagnetic spectrum. An energy of 10 kcal mol⁻¹ corresponds to 3530 cm⁻¹, also in the IR region. Light of wavelength 2000 Å is at the lower end of the UV region (see Figure 11.15) and corresponds to 143 kcal mol⁻¹. Light in the UV and visible region can excite molecules to higher electronic states. Wavelengths in the UV are usually expressed in nanometers (1 nm = $1 \text{ m}\mu = 1 \times 10^{-7} \text{ cm}$), and the UV region is 200-400 nm.

Violet Red						
UV	Near U	UV Vis.	1	IR		
10	200	400	800	2860	28600	$v (m\mu = nm)$
2860	143	71.5	35.75	10	1	E (kcal mol-1)
11972	598.6	299.3	149.7	41.86	4.186	E (KJ mol ⁻¹)
100	2000	4000	8000	2.86 x 10 ⁴	2.86 x 10 ⁵	λ(Å)
1000 x 10 ³	50 x 10 ³	25 x 10 ³	12.5 x 10 ³	3530	353	$v(cm^{-1})$

Figure 11.15. A Portion of the Electromagnetic Spectrum.

How does one know what wavelength of light to use for a particular molecule? Each functional group absorbs light according to its individual structure. If that absorption is in the UV or the IR, a UV spectrum or an IR spectrum can be obtained to determine the maximum wavelength of

^{335.} DePuy, C.H.; Chapman, O.L. *Molecular Reactions and Photochemistry*, Prentice-Hall, Englewood Cliffs, New Jersey, **1972**, p 5.

light absorbed. Ultraviolet light is probably used most often, and the wavelength of maximum absorption (λ_{max}) is a good guide as to which wavelength of light should be chosen for irradiation. Table 11.9³³⁶ shows the energy of absorption in the UV (λ_{max}) for several common types of organic molecules, along with the energy in kcal mol¹ and kJ mol⁻¹.

<u>Molecule</u>	Transition	<u>λ_{max} (nm)</u>	<u>E (kcal mol⁻¹)</u>	<u>E (kJ mol⁻¹)</u>
C ₄ H ₉ I	$n \rightarrow \sigma^*$	224	127.7	534.6
CH ₂ =CH ₂	$\neq \rightarrow \neq^*$	165	173.3	725.4
HC=CH	$\neq \rightarrow \neq^*$	173	165.3	691.9
acetone	$\neq \rightarrow \neq^*$	150	190.7	798.3
	$n \rightarrow \sigma^*$	188	152.1	636.7
	$n \rightarrow \neq^*$	279	102.5	429.1
CH ₂ =CHCH=CH ₂	$\neq \rightarrow \neq^*$	217	131.8	551.7
CH ₂ =CHCHO	$\neq \rightarrow \neq^*$	210	136.2	570.1
	$n \rightarrow \neq^*$	315	90.8	380.1
benzene	$\neq \rightarrow \neq^*$	180	158.9	665.2
		200	143.0	598.6
		255	112.2	469.7
Functional Group	λ _{max} (I	nm) E	(kcal mol ⁻¹)	E (kJ mol ⁻¹)
<u>Functional Group</u> RCH=CHR	<u>λ</u> max_(1 165	<u>nm) E</u>	<u>(kcal mol⁻¹)</u> 173.3	<u>E (kJ mol⁻¹)</u> 725.4
<u>Functional Group</u> RCH=CHR	<u>λ</u> max (1 165 193	<u>nm) E</u>	(kcal mol⁻¹) 173.3 148.2	<u>E (kJ mol⁻¹)</u> 725.4 620.4
Functional Group RCH=CHR RC=CR	<u>λ_{max} (</u> 165 163 193 173	<u>nm) E</u>	(kcal mol ⁻¹) 173.3 148.2 165.3	<u>E (kJ mol⁻¹)</u> 725.4 620.4 691.9
Functional Group RCH=CHR RC=CR R(C=O)R'	<u>λ</u> max (1 165 193 173 188	<u>nm) E</u>	(kcal mol ⁻¹) 173.3 148.2 165.3 152.1	<u>E (kJ mol⁻¹)</u> 725.4 620.4 691.9 636.7
Functional Group RCH=CHR RC≡CR R(C=O)R'	<u>λ</u> max (1 165 193 173 188 279	<u>nm) E</u>	(kcal mol ⁻¹) 173.3 148.2 165.3 152.1 102.5	<u>E (kJ mol⁻¹)</u> 725.4 620.4 691.9 636.7 429.1
Functional Group RCH=CHR RC≡CR R(C=O)R' RCHO	<u>λ</u> max (1 165 193 173 188 279 290	<u>1m) E</u>	(kcal mol ⁻¹) 173.3 148.2 165.3 152.1 102.5 98.6	<u>E (kJ mol⁻¹)</u> 725.4 620.4 691.9 636.7 429.1 412.7
Functional Group RCH=CHR RC=CR R(C=O)R' RCHO RCOOH	<u>λ</u> max_(1 165 193 173 188 279 290 <20	<u>nm) E</u>	(kcal mol ⁻¹) 173.3 148.2 165.3 152.1 102.5 98.6 <137.5	<u>E (kJ mol⁻¹)</u> 725.4 620.4 691.9 636.7 429.1 412.7 <575.6
Functional Group RCH=CHR RC=CR R(C=O)R' RCHO RCOOH -C=N	<u>λ</u> max_(1 165 193 173 188 279 290 <20 <16	nm) E	(kcal mol ⁻¹) 173.3 148.2 165.3 152.1 102.5 98.6 <137.5 <178.8	E (kJ mol ⁻¹) 725.4 620.4 691.9 636.7 429.1 412.7 <575.6 <748.5
Functional Group RCH=CHR RC=CR R(C=O)R' RCHO RCOOH -C=N -N=N-	<u>λ</u> max_(1 165 193 173 188 279 290 <20 <16 347	<u>nm) E</u>	(kcal mol ⁻¹) 173.3 148.2 165.3 152.1 102.5 98.6 <137.5 <178.8 82.4	E (kJ mol ⁻¹) 725.4 620.4 691.9 636.7 429.1 412.7 <575.6 <748.5 344.9
Functional Group RCH=CHRRC=CR $R(C=O)R'$ RCHO $RCOOH$ $-C=N$ $-N=N-$ $R_2C=N-$	<u>λ</u> max_0 165 193 173 188 279 290 <20 <20 <16 347 190	nm) E	(kcal mol ⁻¹) 173.3 148.2 165.3 152.1 102.5 98.6 <137.5 <178.8 82.4 150.5	E (kJ mol ⁻¹) 725.4 620.4 691.9 636.7 429.1 412.7 <575.6 <748.5 344.9 630.0

Table 11.9.	Absorption	Maxima for	Representative	e Molecules	and Functional	Groups

From this table it is apparent that organic molecules absorb energy in the region of $\sim 80-200$ kcal mol⁻¹, easily accessible by exposure of the molecule to a UV light source. Some molecules can react with far less amounts of energy, undergoing photochemical transformations on exposure to visible light or even IR light.

The wavelength of light absorption and corresponding energy for several common functional

^{336.} Silverstein, R.M.; Bassler, G.C.; Morill, T.C. Spectrophotometric Identification of Organic Compounds, 4th Ed., Wiley, New York, **1981**, pp 308 and 312.

groups is also shown in Table 11.10,³³⁷ along with the bond dissociation energies of that functional group. This table illustrates that the wavelength of light used for irradiation closely matches the amount of energy necessary to rupture a given bond (bond dissociation energy). In this section, the main focus will be on using alkenes and carbonyls in [2+2]-photocycloaddition reactions, where the functional groups generally absorb in the 200-300 nm range (140-90 kcal mol⁻¹, 586-377 kJ mol⁻¹). Many light sources will generate light in this region, usually as a broad band of several wavelengths, although it is easy to obtain a light source where one or two intense wavelengths predominate. A low-pressure sodium lamp, for example, generates light of primarily 589 nm (48.6 kcal mol⁻¹, 203.3 kJ mol⁻¹). Mercury lamps usually generate light at ≈ 253.7 nm (112.7 kcal mol⁻¹, 471.9 kJ mol⁻¹). A low pressure mercury lamp tends to give only this wavelength whereas a high-pressure mercury lamp gives several other intense lines as well.³³⁸ If a molecule is irradiated with a light source generating several intense wavelengths of light, other functional groups in a molecule may absorb the light and react, including the photoproduct. A convenient method for limiting the wavelength of light (and thereby the energy of irradiation) is to filter out higher energy wavelengths (and lower energy if necessary). A filter is inserted between the light source and the reactants and sometimes the reaction vessel, made out of Pyrex[™] glass or quartz glass, is the filter. The filter may be attached to the light source. Table 11.11^{339,340} shows several common filters and their approximate range of light transmission.

_	<u>E</u> ª	<u>E</u> a	_	_	Ē	Ē
Bond	(<u>kcal mol⁻¹)</u>	(<u>kJ mol⁻¹)</u>	<u>Wavelength (nm)</u>	<u>Spectral Region</u>	(<u>kcal mol⁻¹)</u>	(<u>kJ mol⁻¹)</u>
C=O	145	607.0	200		140	586.0
O–H	118	494.0	250		110	460.5
C=C	102	427.0	250		110	460.5
C–H	94	393.5	300		90	376.7
S–H	87	364.2	350		80	334.9
C–O	69	288.8	400	Visible, violet	70	293.0
S–S	63	263.7	400		70	293.0
C–C	58	242.8	50	Visible, blue	62	259.5
			500	Visible, green	54	226.0
			550	Visible, yellow	50	209.0
^a Bon	d Dissociation 1	Energy	600	Visible, red	48	200.9
			650	Visible, red	44	184.2
			1000	-	29	121.4

 Table 11.10. Bond Dissociation Energies and Spectral Regions for Irradiation

^{337.} Johnson, E. in *The Physiology and Pathophysiology of the Skin*, Vol. 8 of *The Photobiology of the Skin: Lasers and the Skin*, Jarrett, A. (Ed.), Academic Press, **1984**, p 2401.

^{338.} Calvert, J.G.; Pitts Jr., J.N. Photochemistry, Wiley, New York, 1966, p 474.

^{339.} Murov, S.L. Handbook of Photochemistry, Marcel Dekker, New York, 1973, pp 107-108.

^{340.} Reference 338, p 748.

Filter	<u>Range (nm)^a</u>	Range (kcal mol ⁻¹)	<u>[kJ mol⁻¹]</u>	<u>E_{max}, nm</u>	(kcal mol ⁻¹)	[<u>kJ mol⁻¹]</u>
Quartz crystal ^b	>200	143	[598.6]	>230	124.3	[520.2]
Vycor ^b	>200	143	[598.6]	~280	102.1	[427.4]
Pyrex ^{(™)b}	>280	102.1	[427.4]	~360	79.4	[332.4]
Lead glass ^b	>290	98.6	[412.4]	~380	75.2	[314.8]
Window glass ^c	>310	92.3	[386.4]	~350	81.7	[342.0]
Schott UV R-310 ^c	275-310	104 - 92.3	[435.3 - 386.4]	310	92.3	[386.4]
Schott UV R-280 ^c	240-320	119.2 - 89.4	[499.0 - 374.2]	280	102.1	[427.4]
Schott UV R-250 ^c	225-300	127.1 - 95.3	[532.0 - 398.9]	250	114.4	[478.9]
Suprasil ^c	>160	178.8	[748.2]	180	158.9	[665.2]
Corning 5850 ^c	280→450	102.1 - 63.6	[427.4 - 266.2]	~360	79.4	[332.4]
Corning 5970 ^c	310→420	92.3 - 68.1	[386.4 - 285.1]	~360	79.4	[332.4]
^a Estimated at 50% transmittance from an absorption curve ^b reference 340 ^c Reference 339						
				1. 11.711	NT NT 1 10	

 Table 11.11. Photochemical Filters and Their Effective Transmittance Range

[Reprinted in part with permission from Calvert, J.G.; Pitts Jr., J.N. *Photochemistry*, Wiley, New York, **1966**, pp. 748. Copyright © **1966** by John Wiley and Sons, Inc.]



Figure 11.16. Energy Transition in an Electronically Excited Molecule. [C.H. Depuy/O.L. Chapman, MOLECULAR REACTIONS AND PHOTOCHEMISTRY, ©1972, pp. 6. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey.]

When a molecule absorbs a photon of light, an electron is promoted from the bonding molecular orbital to an anti-bonding molecular orbital $(n \rightarrow \sigma^*, n \rightarrow \pi^*, \text{ or } \pi \rightarrow \pi^*)$ generating a SOMO. Figure 11.16 illustrates this energy transition.³⁴¹ There are several ways a molecule can dissipate excess energy from an excited state,³⁴² as shown in a Jablonski diagram (Figure 11.17). When the excess energy is lost by emission of light (**radiative deactivation**), the process is termed **fluorescence** (occurs with spin conservation) or **phosphorescence** (occurs with spin inversion). If the deactivation is nonradiative, the transition can occur between two states of the same spin

^{341.} Reference 335, p 6.

^{342.} Margaretha, P. Preparative Organic Photochemistry, Lehn, J.-M. (Ed.), Springer-Verlag, Berlin, 1982, pp 6, 7.

(internal conversion) or with inversion of spin (intersystem crossing). The excess energy is liberated as heat in both cases. Deactivation must occur in such a way that there is no motion of the atoms during the electronic transition (the Franck-Condon principle). Transition occurs when the geometries of the excited and ground state are similar as an absorption (solid curves in Figure 11.18),³⁴² or an emission (dashed curves in Figure 11.18).³⁴²



Figure 11.17. Jablonski Diagram.

In Figure 11.18, (I) represents the $0\rightarrow 0$ transition, which is the most intense for emission and absorption (most probable transition). In Figure 11.18, (II) represents a case where the excited and ground states have different geometries, and the most intense transitions are $0\rightarrow 2'$ and $0'\rightarrow 2$ (the $0\rightarrow 0$ transition is indicated as a point of reference for case II). In both cases, the absorption and emission spectra are approximately mirror images. Therefore, it is possible to estimate the energy difference (ΔE) between the excited and ground states.



Figure 11.18. Correlation Between Absorption (a) and Emission (Fluorescence, f) Spectrum.

The excited state can also interact with another molecule in a bimolecular process³⁴³ via energy transfer

$$A^* + B \longrightarrow B^* + A$$
 11.8

or via exciplex formation

 $A^* + B \longrightarrow A^* : B \qquad 11.9$

Energy transfer occurs when ΔE_{A^*A} is $> \Delta E_{BB^*}$. In this case, an excited molecule in a triplet state can transfer energy to the other molecule which is in the singlet state:

$${}^{3}B_{1} + {}^{1}A_{0} \longrightarrow {}^{1}B_{2} + {}^{3}A_{1}$$
 11.10

This process is important if the rate constant of intersystem crossing $k_{si} \rightarrow_{tr}$ for a given molecule is small, or if direct irradiation of these molecules is inconvenient. This process is the foundation of a sensitized reaction.

In many cases, photon absorption is not facile and a sensitizer (S*) is added to facilitate electron transfer between two molecules,³⁴⁴ as shown for the conversion of D-Y to D• and A-X to A•.³⁴⁵ In these reactions,

S*	+	D–Y	 • S ⁻ +	D∙	+	\mathbf{Y}^+
S*	+	А–Х	 $\overset{\bullet}{\mathrm{S}^{+}}$ +	A∙	+	X-

^{343.} Reference 342, p 8.

^{344.} Eaton, D.F. Pure App. Chem. 1984, 56, 1191.

^{345.} Lazár, M.; Richly', J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology*, C.R.C. Press, *1989*, p 22.
D–Y is an electron-rich species that generates the **sensitizer** (a molecule that donates an electron to S). Reductive fragmentation (S donates an electron to A–X) allows fragmentation of the electron poor (acceptor) species. As seen in Figure 11.19,³⁴⁶ the use of a sensitizer involves transfer of excitation energy from an electronically excited molecule (the sensitizer) to the ground state of another molecule, usually providing a triplet excited state. Singlet excitation energy can be transferred, but the lifetime of single excited states is remarkably short (10⁻⁸ vs. >10⁻⁶ s for triplets).³⁴⁶ Triplet energy transfer requires that the triplet energy of the donor be higher than that of the acceptor molecule by 3 kcal mol⁻¹ (12.6 kJ mol⁻¹) or more. Benzophenone is a common triplet sensitizer. The electron transfer occurs by intersystem crossing ($S_1 \rightarrow T_1$, where *S* is the singlet and *T* is the triplet), which is spin forbidden. Nonetheless, it occurs with great efficiency in molecules such as benzophenone. These processes are illustrated in Figure 11.19.³⁴⁶



Figure 11.19. Singlet to Triplet Intersystem Crossing For Sensitized Reactions. [C.H. Depuy/O.L. Chapman, MOLECULAR REACTIONS AND PHOTOCHEMISTRY, ©1972, pp. 36. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey.]

In the photoinduced electrocyclization reaction of 1,3-butadiene, cyclobutene and bicyclobutane (**361**) are produced via the singlet diene. Photolysis in the presence of triplet excited benzophenone gave the dimers (**362** and **363**) via the triplet diene.³⁴⁷ Irradiation at 366 nm



[C.H. Depuy/O.L. Chapman, MOLECULAR REACTIONS AND PHOTOCHEMISTRY, ©1972, pp. 37. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey.]

(78.1 kcal mol⁻¹, 327.1 kJ mol⁻¹) of a mixture of butadiene and benzophenone led to exclusive absorption by benzophenone. The triplet energy of benzophenone (69 kcal mol⁻¹, 288.8 kJ mol⁻¹) is transferred with 100% efficiency via intersystem crossing $(S_1 \rightarrow T_1)$, due to this small energy gap.³⁴⁸ Triplet butadiene is \approx 60 kcal mol⁻¹ (251.2 kJ mol⁻¹) above the ground state, and the 69 kcal mol⁻¹ (288.8 kJ mol⁻¹) of benzophenone is more than adequate for diffusion

^{346.} Reference 335, p 36.

^{347.} Reference 335, p 37.

^{348.} Reference 335, p 38

controlled energy transfer to butadiene, as shown on the Jablonski diagram in Figure 11.19.³⁴⁶ Since the $S_0 \rightarrow S_1$ energy gap of benzophenone is lower than the $S_0 \rightarrow S_1$ transition for butadiene, transfer between singlet benzophenone and singlet butadiene does not occur.³⁴⁶ Benzophenone is one of many commonly used sensitizers. Others include acetophenone and naphthalene. More exotic sensitizers are known and used, but rose bengal (**364**), chlorophyll a (**365**) and methylene blue (**366**) are readily available and commonly used.



In photochemical reactions, it is important to measure the efficiency of the photolysis, which is done by the parameter known as **quantum yield** (or **quantum efficiency**) defined as the number of molecules reacted or formed per light quanta absorbed.³⁴⁹ The quantum yield for formation of a product (Φ_{form}) is

$$\Phi_{\text{form}} = \frac{\text{No. of molecules of product formed}}{\text{No. of quanta absorbed}}$$
11.11

Quantum yield can also be expressed in terms of the number of molecules of starting material (SM) which disappear per quantum of light (Φ_{dis}) :³⁵⁰

$$\Phi_{\rm dis} = \frac{\rm No. \ of \ molecules \ of \ SM \ destroyed}{\rm No. \ of \ quanta \ absorbed} 11.12$$

For photochemical reactions that give a single product, $\Phi_{form} = \Phi_{dis}$. If several products are formed, however, $\Phi_{dis} = \Sigma \Phi_{form}$. If a reaction does *not* go through a chain mechanism, Φ will have a value between 0 and 1. Free radical chain mechanisms have quantum yields as high as several thousand,²⁹² which reflects the photochemical initiation step leading to a radical chain carrier molecule or molecules.

^{349.} Reference 335, p 20.

^{350.} Reference 335, p 76.

11.10.C. Photochemical [2+2]-Cycloadditions

[2+2]-Photocycloaddition reactions are quite useful in synthesis, and variations include the cycloaddition of alkenes, alkynes or conjugated carbonyl compounds with other alkenes, alkynes or conjugated systems.³⁵¹ In general, photolysis of enones requires wavelengths > 3000Å (300 nm, 95.3 kcal mol⁻¹, 399.1 kJ mol⁻¹), corresponding to the $n \rightarrow \pi^*$ transition.³⁵² This reaction is usually accomplished by photolysis in a Pyrex container, which is opaque to light < 300 nm. The $n \rightarrow \pi^*$ transition for acrolein occurs at 315 nm (90.8 kcal mol⁻¹ = 380.1 kJ mol⁻¹; the λ_{max} for acrolein).³⁵³ Ethene, however, has a strong $\pi \rightarrow \pi^*$ transition at ≈ 165 nm. In general, irradiation of alkene must use higher energy (165 nm, 173.3 kcal mol⁻¹ = 725.4 kJ mol⁻¹) to populate the LUMO. There are countless synthetic examples. In one, taken from Sorensen and Shipe's synthesis of guanacastepene,³⁵⁴ irradiation of **367** in a mixture of Hünig's base and ether led to a 76% yield of cyclobutane derivative **368**.



Hammond and Liu studied this type of photocyclization and showed that myrcene (**369**) cyclized to **370** in the presence of a benzophenone sensitizer.³⁵⁵ Direct (unsensitized) photocyclization of **369** gave primarily **371**, and a small amount of β -pinene (**372**).³⁵⁶ Photolysis in the presence of the benzophenone sensitizer leads to a triplet diradical intermediate, whereas the direct photolysis generated an excited diene that does not cross to the triplet manifold (see above) prior to cyclization.



There are many examples of photochemical [2+2]-cycloadditions involving enones and alkenes, or alkenes with alkenes. Solvent-controlled intramolecular [2+2] photocycloadditions of

- 355. Liu, R.S.H.; Hammond, G.S. J. Am. Chem. Soc. 1964, 86, 1892.
- 356. Crowly, K.J. Proc. Chem. Soc. 1962, 245, 334.

^{351.} For a review of intermolecular reactions in synthesis, see Bach, T. Synthesis 1998, 683.

^{352.} Eaton, P.E. Acc. Chem. Res. 1968, 1, 50.

^{353.} Reference 335, p 308.

 ⁽a) Shipe, W.D.; Sorensen, E.J. Org. Lett. 2002, 4, 2063; (b) Shipe, W.D.; Sorensen, E.J. J. Am. Chem. Soc. 2006, 128, 7025.

 α -substituted enones have been studied.³⁵⁷ The conversion of **367** to **368** is an example of the reaction with conjugated carbonyl compounds, and an example of the latter is taken from Hsung and co-worker's synthesis of rhododaurichromanic acid A,³⁵⁸ in which **373** was photolyzed to give a 79% yield of **374** as a 1:1 mixture of isomers (at methyl). Williams and Callahan used this reaction in a synthesis of shyobunone,³⁵⁹ and Wender and Lechleiter synthesized 10-epijuneol by a similar route.³⁶⁰ It should be noted that selectivity may be an issue for intermolecular reactions, and a cyclohexenone derivative reacting with 1- or 2-butene will give a mixture of diastereomers.



It is apparent from these examples that the cycloaddition can be highly stereoselective, and asymmetric intramolecular [2+2]-photocycloaddition reactions are known. One example used chiral α - and β -hydroxy acids³⁶¹ as tether groups to direct the stereochemistry of the cycloaddition. The relative stereochemistry observed in many [2+2]-photocycloadditon reactions generally corresponds to a suprafacial addition for both alkene fragments.³⁶²

For intermolecular reactions, free rotation around the original carbon-carbon double bond can take place in the excited state of the molecule, although not in the intramolecular reaction that formed **374**. Because of such rotation, photocyclization of 2-butene leads to four tetramethylcyclobutane isomers (**375-378**).³⁶² Similar results are observed when unsymmetrical alkenes are photocyclized. Selectivity is improved with stereochemically pure alkenes. Reaction of pure *cis*-2-butene gave only **375** and **376** with complete retention of configuration. Similarly, pure *trans*-2-butene gave only **377** and **378**. In general, reaction of an alkene and a conjugated carbonyl derivative gives a derivative such as **379**, and coupling of two nonconjugated alkenes gives **380**. Despite the selectivity shown in the reaction of 2-butene, the relative proportions of cis and trans cycloadduct may depend on the reaction conditions. Eaton^{352,363} showed that irradiation of cyclopentene gave a mixture of **381** (the head-to-head dimer) and **382** (the head-to-tail dimer). Both the molarity of cyclopentene and the solvent were varied (see Table 11.12).^{352,263} The head-to-tail cycloadduct (**382**) was the

^{357.} Ng, S. M.; Bader, S. J.; Snapper, M. L. J. Am. Chem. Soc. 2006, 128, 7315.

^{358.} Kurdyumov, A.V.; Hsung, R.P.; Ihlen, K.; Wang, J. Org. Lett. 2003, 5, 3935.

^{359.} Williams, J.R.; Callahan, J.F. J. Chem. Soc. Chem. Commun. 1979, 404.

^{360.} Wender, P.A.; Lechleiter, J.C. J. Am. Chem. Soc. 1978, 100, 4321.

^{361.} Faure, S.; Piva-Le-Blanc, S.; Bertrand, C.; Pete, J.-P.; Faure, R.; Piva, O. J. Org. Chem. 2002, 67, 1061.

^{362.} Yamazaki, H.; Cvetanović, R.J. J. Am. Chem. Soc. 1969, 91, 520.

^{363.} Eaton, P.E. J. Am. Chem. Soc. 1962, 84, 2344, 2454.

major product in all cases, but the selectivity varied with reaction conditions. The ratio of dimers was independent of the method of triplet generation, independent of the concentration of the sensitizer and quencher and was unaffected by the presence of excess reactant. The solvent had an effect, and the concentration effect was more pronounced in nonpolar solvents. The regiochemistry of the cycloaddition was controlled by the orbital coefficients.³⁶⁴ The interaction of the largest coefficients predicted the regiochemistry, and chemoselectivity can also be predicted.



Table 11.12. Influence of Solvent and Concentration on the Photocyclization ofCyclopentenone

o L	hν (Pyre	\xrightarrow{O}_{H}	$H = 0 \qquad H = H \qquad H = $	$\overline{\langle}_{0}$	
<u>Solvent</u>	<u>Molarity</u>	<u>370:371</u>	<u>Solvent</u>	<u>Molarity</u>	<u>370:371</u>
neat	12.4	43:57	<i>t</i> -BuOH	1.0	24 : 76
PhH	10.0	41:59	EtOAc	1.0	30:70
	5.0	35:65	dimethyl 1,4-dcyclohexane	•	
	2.0	27:73	dicarboxylate	1.0	33:67
	1.1	23:77	МеОН	10.5	41 : 59
	0.093	15:85		1.0	41 : 59
PhH-cyclopentanone	1.0	27:73		0.1	39:61
[Reprinted with permiss Chemical Society.]	sion from Ea	ton, P.E. Accts	. Chem. Res. 1968 , 1, 50. Copyr	ight © 1968 A	merican

^{364.} Servé, P.; Rosenberg, H.M.; Rondeau, R. Can. J. Chem. 1969, 47, 4295.

Intramolecular alkene cycloadditions can be used to generate quaternary centers and for construction of highly bridged molecules. We saw examples in the photocyclization of **367** and of **373**. Another example is taken from Sulikowski and Dohroh's synthesis of the tetracyclic

core of bielschowskysin A, in which conjugated lactone **383** was photolyzed to give a 50% yield of **384**.³⁶⁵ Note that the stereochemistry of the spirocyclic lactone is determined by bond rotation in triplet biracial intermediates.



Electrocyclic ring closure (see section 11.11) can occur in diene systems, even with small rings. Photolysis of 2-pyridone **385**, for example, gave **386**. Unmasking the enol with fluoride gave the carbonyl,³⁶⁶ and reduction with cyanoborohydride (sec. 4.5.D) gave the interesting and useful β -lactam **387**.



[2+2]-photocycloaddition and electrocyclic reactions of alkenes allow the following disconnections:



11.10.D. The Paternò-Büchi Reaction

[2+2]-Photocyclization is not limited to two alkene partners, and one important reaction involves cycloaddition of a carbonyl and an alkene. This reaction was discovered by Paternò

^{365.} Doroh, B.; Sulikowski, G.A. Org. Lett. 2006, 8, 903.

^{366. (}a) Sato, M.; Katagiri, N.; Muto, M.; Haneda, T.; Kaneko, C. *Tetrahedron Lett.* **1986**, 27, 6091; (b) Kaneko, C.; Katagiri, N.; Sato, M.; Muto, M.; Sakamoto, T.; Saikawa, S.; Naito, T.; Saito, A. *J. Chem. Soc. Perkin Trans.* **1 1986**, 1283.

and Chieffi in 1909³⁶⁷ and expanded by Büchi et al.;³⁶⁸ thus it is called the **Paternò-Büchi reaction**.³⁶⁹ The product is an oxetane (**389**), and the reaction is believed to proceed via a diradical intermediate (**388**). The regioselectivity of the reaction can be explained by molecular orbital considerations, however. Electron- rich carbonyls of aldehydes or ketones

$$\begin{array}{c} O \\ R \xrightarrow{I} R^{1} + R^{2} \xrightarrow{hv} R^{3} \xrightarrow{hv} \left[\begin{array}{c} O \\ R \xrightarrow{I} R^{1} R^{2} \\ 388 \end{array} \right] \xrightarrow{V} R^{1} R^{3} \\ 389 \end{array}$$

can be used. The alkene moiety is usually electron rich but this is not a requirement. A synthetic example that also illustrates the intramolecular

version of the reaction is Greaney and co-worker's synthesis of merrilactone A, in which **390** was photolyzed to give a 93% yield of oxetane **391** where the ketone carbonyl cyclized to the C=C unit of the conjugated ketone moiety.³⁷⁰ Irradiation of aldehydes such as this

often uses light at 290 nm (98.6 kcal mol⁻¹; 412.8 kJ mol⁻¹), generally corresponding to the $n \rightarrow \pi^*$ transition of the carbonyl. Lower energy irradiation can also be used, however, such as laser irradiation in the visible region (445-515 nm, 64.3-55.5 kcal mol⁻¹, 269.2-232.3 kJ mol⁻¹).³⁷¹ Intramolecular Paternò-Büchi reactions are used in other natural product synthesis.³⁷²



This reaction can be done in the presence of a rather wide range of functionality. It has been used with aromatic compounds such as 2-furylmethanol derivatives, as in the reaction of 392^{373} with benzophenone to give a 65% yield of **393** along with a 20% yield of **394**. The photocycloaddition product of the Paternò-Büchi reaction with these substrates is an acetal or a ketal, and it can be hydrolyzed to produce acyl derivatives or other functionality. This synthetic route is attractive since achiral fragments generate cycloadducts with several contiguous chiral centers whose relative stereochemistry can usually be predicted with great accuracy.



- 367. Paternò, E.; Chieffi, C. Gazz. Chim. Ital. 1909, 39, 341.
- 368. Büchi, G.; Inman, C.G.; Lipinsky, E.S. J. Am. Chem. Soc. 1954, 76, 4327.
- 369. (a) Reference 65, pp 912-913; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-69; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 484-485.
- 370. Iriondo-Alberdi, J.; Perea-Buceta, J.E.; Greaney, M.F. Org. Lett. 2005, 7, 3969.
- 371. Adam, W.; Kliem, U.; Mosandl, T.; Peters, E.M.; Peters, K.; von Schnering, H.G.J. Org. Chem. 1988, 53, 4986.
- 372. de la Torre, M.C.; García, I.; Sierra, M.A. J. Org. Chem. 2003, 68, 6611.
- 373. D'Auria, M.; Racioppi, R.; Romaniello, G. Eur. J. Org. Chem. 2000, 3265.

The Paternò-Büchi disconnection is



11.10.E. [2+2]-Cycloreversion Reactions

The reverse of the [2+2]-cycloaddition is a thermally allowed $\sigma_{2s} + \sigma_{2a}$ cycloreversion.³⁷⁴ Conversion of **395** to alkenes **397** and **398** illustrates this process. Note that the geometry of one alkene precursor is retained (suprafacial ring opening), but the other is reversed (antarafacial ring opening represented by **396**).³⁷⁵ The thermal process requires interaction of a HOMO and a LUMO, which must proceed via the antarafacial ring opening represented by **396**.



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An example is the photochemical [2+2]-cycloaddition to form **399**, which is followed by thermal ring opening with cleavage of either cyclobutane moiety (**path** *a* or **path** *b*). **Path** *a* leads to a 10-membered ring diene (**400**), and path *b* to the monocyclic diene (**401**).³⁷⁶



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^{374.} Reference 80b, pp 77-83.

^{375.} Reference 80b, p 77.

^{376. (}a) Reference 80b, p 77; (b) see Wender, P.A.; Lechleiter, J.C. J. Am. Chem. Soc. 1977, 99, 267.

The pathway taken by the reaction appears to depend on the substituents. Cycloaddition of ketone **402** with methylcyclobutene generates derivatives such as **403**, with alkyl substituents at the bridgehead positions. Upon heating, cycloadducts of this type open to give **404** (shyobunone), an elemane sesquiterpene, although the yield here was only 5% yield of **404**,^{377,259} however, which contrasts with **406** that was formed from methyl cyclobutenecarboxylate and cyclohexenone **405**. Cycloadduct **406** contains an ester moiety, and upon heating it opened to give the germacradiene sesquiterpene isabelin (**407**) in the synthesis reported by Wender and Lechleiter.³⁷⁸



Typical cycloreversion disconnections are



11.11 ELECTROCYCLIC REACTIONS

Woodward and Hoffmann defined electrocyclic transformations³⁷⁹ as "the formation of a single bond between the termini of a linear system containing $k \pi$ -electrons (408 \rightarrow 409), and the converse process".³⁸⁰ Electrocyclic reactions³⁸¹ involve an equilibrium between a ring-closed

- 380. Woodward, R.B.; Hoffmann, R. J. Am. Chem. Soc. 1965, 87, 395.
- 381. See *Electrocyclic Reactions*, Ansari, F.L.; Quereshi, R.; Quereshi, M.L. Wiley-VCH, Weinheim, New York, *1999*.

^{377.} Williams, J.R.; Callahan, J.F. J. Org. Chem. 1980, 45, 4475.

^{378.} Wender, P.A.; Lechleiter, J.C. J. Am. Chem. Soc. 1980, 102, 6340.

^{379.} For a review of biosynthetic and biomimetic electrocyclizations, see Beaudry, C.M.; Malerich, J.P.; Trauner, D. Chem. Rev. 2005, 105, 4757.

and a ring-opened molecule that are structurally related. The reaction, which occurs within one molecule, involves the interconversion of a σ -electron system to a π -electron system. This section will explore synthetically useful electrocyclic reactions.



[Reprinted with permission from Woodward, R.B.; Hoffmann, R. *J. Am. Chem. Soc.* **1965**, 87, 395. Copyright © 1965 American Chemical Society.]

11.11.A. Cyclobutene Ring Opening

Thermal and photochemical ring opening reactions of cyclobutenes (**410** and **413**) are electrocyclic reactions. Although both (*E*,*E*) and (*E*,*Z*) dienes are possible by opening a cyclobutene ring, cis disubstituted cyclobutenes (**410a**) give only the (*E*,*Z*) diene (**411**) under thermal conditions, and only the (*E*,*E*) diene (**412**) photochemically. Opening of **410** can proceed via a conrotatory process (**410a**) to give **411**, or a disrotatory process (**410b**) to give **412**. Experimental results suggest that the thermal process is conrotatory and the photochemical process is disrotatory. Similarly, thermal conrotatory ring opening of **413a** leads to **414**, and photochemical disrotatory ring opening (**413b**) leads to **415**.³⁸² An example is the pyrolysis of cyclobutene **417** to give substituted butadiene derivative **418**. Cyclobutene derivatives can be prepared by several routes. In this example, cyclobutene **417** was prepared from cyclopropylcarbinyl alcohol **416** by treatment with SOBr₂ at 100°C,³⁸³ or aqueous HBr/ZnBr₂³⁸⁴ followed by heating with copper triflate and Hünig's base. Heating **417** [with thionyl bromide at 100°C³⁸³ or via FVP³⁸⁴] opened the ring to the *S*-phenylthiobutadiene derivative (**418**).



^{382.} Reference 10b, pp 38-46.

- 383. Trost, B.M.; Jungheim, L.N. J. Am. Chem. Soc. 1980, 102, 7910.
- 384. Kwon, T.W.; Smith, M.B. Chem. Lett. 1989, 2027.



A related reaction has been applied to several natural product syntheses, primarily in work reported by Oppolzer³⁸⁵ and Kametani Nemoto.³⁸⁶ In these cases benzocyclobutene derivatives

(419) open upon heating to form a transient diene (420) that is highly reactive in Diels-Alder reactions because formation of the cycloadduct regenerates the aromatic ring. This method is powerful for constructing polycyclic ring systems, and the



use of amide cyclobutane derivatives leads to heterocyclic alkaloids. The structure of the ring bearing the heteroatom is dependent on the type of amide (as seen previously in sec. 11.7). Heating **421**, for example, gave the trans-adduct **422** in 90% yield but **423** gave the cis-adduct **424** in 78% yield.³⁸⁷ Amide **421** has the carbonyl within the ring being formed, whereas **423** has the carbonyl external to the ring being formed. This methodology was used in Oppolzer and Keller's synthesis of chelidonine.^{387a} The presence of a nitrogen atom attached to the cyclobutane unit is not required for the reaction, and other alkaloids can be produced when the nitrogen atom is moved away from the cyclobutane unit.³⁸⁸ Nitrogen does not have to be present in the substrate. In a synthesis of viridin,³⁸⁹ Sorensen and co-workers heated benzocyclobutene **425** in degassed xylenes, to give an 83% yield of **426**. Sorensen suggested that the silyl ether substituent conferred a high degree of torquoselectivity³⁹⁰ to the ring-opening process.



- 386. Kametani, T.; Nemoto, H. Tetrahedron 1981, 37, 3.
- 387. (a) Oppolzer, W.; Keller, K. J. Am. Chem. Soc. 1971, 93, 3836; (b) Oppolzer, W. Tetrahedron Lett. 1974, 1001.
- 388. Verrat, C.; Hoffmann, N.; Pete, J.P. Synlett 2000, 1166.
- 389. Anderson, E.A.; Alexanian, E.J.; Sorensen, E.J. Angew. Chem. Int. Ed. 2004, 43, 1998.
- 390. (a) Rondan, N.G.; Houk, K.N. J. Am. Chem. Soc. 1985, 107, 2099; (b) Houk, K.N.; Spellmeyer, D.C.; Jefford, C.W.; Rimbault, C.G.; Wang, Y.; Miller, R.D. J. Org. Chem. 1988, 53, 2125.

^{385.} Oppolzer, W. Synthesis 1978, 793.



The cyclobutene ring opening disconnections are



11.11.B. Hexatriene Derivatives and Related Compounds

Another useful electrocyclic reaction is the interconversion of 1,3,5-hexatriene (427) to cyclohexadiene (428). Woodward and Hoffmann categorized the thermal cyclization of hexatrienes as uniquely disrotatory, but a stereospecific conrotatory process is observed under photochemical conditions.³⁸⁰ This is supported by orbital and state correlation diagrams of Longuet-Higgins and Abrahamson.³⁹¹



 6π -Electrocyclic reactions have been used many times in synthesis,³⁹² often combined with other structural features to generate interesting structures. In a synthesis of dihydrospiniferin-1 by Marshall and Conrow,³⁹³ treatment of **429** with DDQ gave the dehydrogenated product **430**,

^{391.} Longuet-Higgins, H.C.; Abrahamson, E.W. J. Am. Chem. Soc. 1965, 87, 2045.

^{392.} Nicolaou, K.C.; Sasmal, P.K.; Xu, H. J. Am. Chem.Soc. 2004, 126, 5493. For an example taken from a synthesis of 9,10-deoxy-tridachione, see Rodriguez, R.; Adlington, R.M.; Eade, S.J.; Walter, M.W.; Baldwin, J.E.; Moses, J.E. Tetrahedron 2007, 63, 4500.

^{393.} Marshall, J.A.; Conrow, R.E. J. Am. Chem. Soc. 1980, 102, 4274.

which upon treatment with aqueous acid generated enol **431**. Electrocyclic ring opening gave **432**, which led to **433**, isolated in 74% yield.

This type of electrocyclic ring close is not limited the carbocyclic systems. Parker and Mindt showed that enolizable vinyl quinone imides were converted to dihydroisoquinolines by thermal 6π -electrocyclization.³⁹⁴ Specifically, quinone imide **434** enolized to **435** *in situ*, and 6π -electrocyclization gave **436** in 55% yield.



The electrocyclization has been extended to other π -systems. Okamura and co-worker's reported an 8π -electron electrocyclization reaction in the synthesis of an analog of 1α ,25-dihydroxyvitamin D₃.³⁹⁵ Lindlar hydrogenation of the triple bond in **437** generated **438**, which was a transient product immediately undergoing the 8π electrocyclization to give **439** in 50% yield.



11.12 [3+2]-CYCLOADDITION REACTIONS

We have seen both [4+2]- and [2+2]-cycloaddition reactions in previous sections. There is another class of cycloaddition reactions that involve a molecule containing a π bond (an alkene, alkyne, etc., see **441**) and a highly polarized, and often ionic compound, that is called a 1,3-dipole. 1,3-Dipoles usually take the form of **440**. When these two react, a five-membered ring is generated. Depending on the nature of *a-e*, carbocyclic or heterocyclic rings can be

^{394.} Parker, K.A.; Mindt, T.L. Org. Lett. 2002, 4, 4265.

^{395.} Hayashi, R.; Fernández, S.; Okamura, W.H. Org. Lett. 2002, 4, 851.

formed, and a variety of substituents can be incorporated on the ring.³⁹⁶ This section will explore this class of reactions, which are particularly useful for the synthesis of heterocyclic compounds and natural products.³⁹⁷



11.12.A. Dipoles and Dipolarophiles

Cycloaddition reactions that involve dipolar species such as 440 (called 1.3-dipoles), reacting with π -bonds [called **dipolarophiles** (441)] to give five-membered rings (442) are often called 1,3-dipolar cycloadditions. Formally, the reaction is a [3+2]-cycloaddition. A 1,3-dipole usually contains heteroatoms, and it usually contains four π -electrons distributed over three atoms. The dipolarophile is commonly an alkene or alkyne derivative. Huisgen showed that the rate of bimolecular reactions is not greatly influenced by the dielectric constant of the solvent, and proceeds with high stereo- and regioselectivity.^{398,399} The reaction is believed to proceed by a concerted, thermal cyclization.⁴⁰⁰ It is noted that Firestone has proposed a two step diradical mechanism.⁴⁰¹ Cossío, Schleyer and co-workers studied these cycloaddition reactions computationally, and found that the transition structures associated with concerted suprasupra processes are in-plane aromatic, but aromaticity does not determine regiochemistry.⁴⁰² Electrostatic interactions and solvent effects can modify the regiochemical and stereochemical outcome.⁴⁰² In a computational study of the 1.3-dipolar cycloaddition of nitrones to alkenes. Di Valentin et al.⁴⁰³ found that the concerted path (Huisgen's mechanism)³⁹⁸ should overwhelm the stepwise diradical mechanism proposed by Firestone.⁴⁰¹

Both intermolecular cycloadditions (440 \rightarrow 442) and intramolecular reactions $(443 \rightarrow 444)$ are possible. An isomeric bridged cycloadduct (445) can be produced in this latter reaction if the tether is long enough. Padwa reviewed the



internal [3+2]-cycloaddition reaction,⁴⁰⁴ as did Oppolzer.⁴⁰⁵

(a)Reference 7, pp 148-161; (b) Reference 80b, pp 89-117. 399.

404. Padwa, A. Angew. Chem. Int. Ed. 1976, 15, 123

^{396.} For a review of pyrrolizidine and indolizidine alkaloid syntheses involving 1,3-dipolar cycloadditions, see Broggini, G.; Zecchi, G. Synthesis, 1999, 905.

Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products, 397. Padwa, A.; Pearson, W.H. (Eds), Wiley, New York, Chichester, 2003.

⁽a) Huisgen, R. J. Org. Chem. 1968, 33, 2291; (b) Idem Angew. Chem. Int. Ed. 1963, 2, 565, 633. 398.

⁽a) Hoffman, R.; Woodward, R.B. Acc. Chem. Res. 1968, 1, 17; (b) Eckell, A.; Huisgen, R.; Sustmann, R.; 400. Wallbillich, G.; Grashey, D.; Spindler, E. Chem. Ber. 1967, 100, 2192.

⁽a)Firestone, R.A.J. Org. Chem. 1968, 33, 2285; (b) Idem Ibid. 1972, 37, 2181; (c) Idem J. Chem. Soc. A 1970, 1570. 401.

Cossío, F.P.; Morao, I.; Jiao, H.; Schleyer, P.v.R. J. Am. Chem. Soc. 1999, 121, 6737. 402.

^{403.} Di Valentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. J. Org. Chem. 2000, 65, 6112.

^{405.} Reference 236 (see p 18-22).

This type of dipolar addition reaction was introduced in chapter 3 in connection with ozonolysis (sec. 3.7.B), as well as permanganate (sec. 3.5.A)⁴⁰⁶ and osmium (sec. 3.5.B) dihydroxylation of alkenes. Ozone is a classical example of a dipolar molecule (see canonical forms of **446**, ⁺O-O-O⁻ and ⁻O-O-O⁺). The [3+2]-cycloaddition of ozone with ethene is controlled by interaction of the frontier molecular orbitals.⁴⁰⁷ Interactions of the HOMO of ozone with the LUMO of the alkene, and of the LUMO of ozone with the HOMO of the alkene are symmetry allowed.⁴⁰⁸ There are three possible orbital interactions, proposed by Sustmann.^{409,400b} Substituents that raise the dipole HOMO energy or lower the LUMO energy of the dipolarophile will accelerate the reaction controlled by HOMO_{dipole}-LUMO_{dipolarophile}.^{400b} Substituents that lower the dipole LUMO energy or raise the HOMO energy of the dipolarophile will accelerate the reaction controlled by LUMO_{dipolarophile}.^{400b}

As discussed in Section 3.7.B, ozone adds to an alkene to generate a 1,2,3-trioxolane. Addition of ozone to 1-pentene, for example, generated **447**. Rearrangement of this initially formed cycloadduct is facile, even at temperatures as low as -78° C, and results in cleavage of the carbon-carbon bond in **447** with formation of a 1,2,4-trioxolane (**448**). This product is usually called an ozonide and can be either oxidized or reduced to give the carbonyl compounds characteristic of the oxidative or reductive cleavage reactions.



There are many types of 1,3-dipoles other than ozone (see Table 11.13).⁴¹⁰ A few synthetically useful examples are diazoalkanes (**449**, secs. 13.9.B.ii, 13.9.C), nitrile ylids (**450**), nitrile oxides (**451**), azides (**452**), azomethine ylids (**453**), nitrones (**454**) and carbonyl ylids (**455**). The HOMO-LUMO values for these dipolar compounds, and their orbital coefficients at the terminal atoms as shown in Table 11.13,⁴¹⁰ taken largely from Houk's work but also from work by Bastide and Henri-Rouseau.⁴¹¹ When the energies and orbital coefficients of the alkene LUMO (from Table 11.1) are used with Table 11.13, reactivity and regioselectivity can be predicted.

^{406.} Houk, K.N.; Strassner, T. J. Org. Chem. 1999, 64, 800.

^{407. (}a) Caramella, P.; Gandour, R.W.; Hall, J.A.; Deville, C.G.; Houk, K.N. *I. Am. Chem. Soc.* 1977, 99, 385;
(b) Houk, K.N.; Sims, J.; Watts, C.R.; Luskus, L.J. *Ibid.* 1973, 95, 7301.

^{408.} Reference 7, p 93.

^{409.} Sustmann, R. Tetrahedron Lett. 1971, 12, 2717.

^{410.} Reference 7, pp 148-149.

⁽a) Houk, K.N.; Sims, J.; Duke Jr., R.E.; Strozier, R.W.; George, J.K. J. Am. Chem. Soc. 1973, 95, 7287;
(b) Bastide, J.; Ghandour, N.E.; Henri-Rousseau, O. Bull. Chim. Soc. Fr. 1973, 2290, 2294; (c) Bastide, J.; Henri-Rousseau, O. Ibid. 1973, 2294; (d) Idem Ibid. 1974, 1037.



Table 11.13 HOMO and LUMO Energies and Orbital Coefficients of Common 1,3-Dipoles

	HOMO LUMO	$\mathbf{R}^{1} - \mathbf{X} - \mathbf{c}_{1}$ \mathbf{c}_{3}	Y — Z c c	L 2 4			
Dipole	<u>X-Y-Z</u>	HOMO	<u>c1</u>	<u>c2</u>	HOMO	<u>c3</u>	<u>c4</u>
ozone	$^{+}O_{-}O_{-}O^{-}$	-13.5			-2.2		
nitrile ylid	$HC = N^+ - CH_2^-$	-7.7	1.07	1.50	0.9	0.69	0.64
nitrile oxide	$HC = N^+ - O^-$	-11.0	0.81	1.24	-0.5	1.18	0.17
diazoalkanes	$H_2C=N^+=N^-$	-9.0	1.57	0.85	1.8	0.66	0.56
azides	$HN=N^+=N^-$	-11.5	1.56	0.72	0.1	0.37	0.76
azomethine ylids	$H_2C=NH^+-CH_2^-$	-6.9	1.28	1.28	1.4	0.73	0.73
nitrones	$H_2C=NH^+-O^-$	-9.7	1.11	1.06	-0.5	0.98	0.32
[Reprinted with permi Wiley, London, 1976,	ssion from Fleming, I. pp. 148-149. Copyrigh	Frontier Mol nt © 1976 by	<i>ecular Or</i> John Wil	<i>bitals an</i> ey and So	d Organic Ch ons, Inc.]	emical R	eactions,

11.12.B. Nitrile Ylids

Frontier molecular orbital analysis is illustrated by reaction of nitrile ylid **456**⁴¹² with ethene, methyl acrylate or methyl vinyl ether as diagrammed in Figure 11.20⁴¹² (all HOMO and LUMO values and coefficients are from Table 11.1). The ΔE values from Figure 11.20 suggest that nitrile ylids should react fastest with electron-deficient alkenes and slowest with electron-rich alkenes, similar to the normal electron demand found in Diels-Alder reactions. If so, there are two possible regioisomers for reaction of **450** with methyl acrylate, **457** and **458**. The orbital coefficients (see **456** and Table 11.1) suggest that **458** is the preferred product. Estimation of the values from Table 11.13 (for H–C=N⁺–CH₂⁻), and the observation that Ph–C=N⁺–CH₂⁻ has a HOMO of –6.4 eV and a LUMO of +0.6 eV,⁴¹³ shows that these values are sensitive to structural modification. Therefore, general predictions of either reactivity or regioselectivity are risky and each case should be considered individually. Electron deficient alkenes have the lowest ΔE for all of the dipoles shown in Table 11.13, and should react fastest.

^{412.} Reference 7, p 93.

^{413.} Reference 7, p 148.



Figure 11.20. The HOMO-LUMO Interactions of Nitrile Ylid With Alkenes. [Reprinted, in part, with permission from Fleming, I. *Frontier Molecular Orbitals and Organic Chemical Reactions*, Wiley, London, **1976**, p. 151. Copyright © **1976** by John Wiley and Sons, Inc.]



The inverse electron demand ΔE is lower for reaction of ozone, azides or nitrile oxides and suggests that the fastest reactions are with electron-rich alkenes. A synthetic example, taken from a synthesis of *ent*-alantrypinone by Hart and Magomedov,⁴¹⁴ involved thermal fragmentation of **459** to **460**, and rapid proton transfer to give nitrile ylid **461** *in situ*. Subsequent intramolecular [3+2]-cycloaddition with the distal carbonyl gave an 80% yield of **462**. This example not only illustrates an intramolecular variation, but also that carbonyls can serve as the dipolarophile.



^{414.} Hart, D.J.; Magomedov, N.A. J. Am. Chem. Soc. 2001, 123, 5892.



The typical nitrile ylid disconnection is



11.12.C. Nitrile Oxides

Frontier molecular orbital theory predicts that nitrile oxides should react faster with electron-rich alkenes (vinyl ethers, enamines or even simple alkenes). The orbital coefficients suggest (see Tables 11.1 and 11.22) that propene reacts with **463** (HOMO_{dipole}-LUMO_{dipolarophile}) to give **464**. The regiochemistry of the product depends on the substrate, but substituents on the alkene are usually adjacent to the oxygen in the product. Products in which an alkyl substituent is adjacent to a carbon that bears an electron-releasing group (such as methyl vinyl ether to give **465**), or an electron-withdrawing group are usually preferred. In a synthesis of (+)-calafianin,⁴¹⁵ Porco and co-workers generated nitrile oxide **467** *in situ* from the acyl oxime shown⁴¹⁵ (generated from ethyl chlorooximinoacetate and diisopropylethylamine via EtO₂CC(Cl)=NOH).⁴¹⁶ The [3+2]-cycloaddition with **466** gave a 1.8:1 mixture of isoxazolines **468** and **469** in 85-93% yield.⁴¹⁵ The use of bases such as DBU or KHCO₃ led to very poor yields of isoxazolines, but good yields were obtained using Kobayashi and co-worker's procedure with zirconium (IV) alkoxides.⁴¹⁷



^{415.} Bardhan, S.; Schmitt, D.C.; Porco Jr., J.A. Org. Lett. 2006, 8, 927.

Blanchette, M.A.; Choy, W.; Davis, J.T.; Essenfeld, A.P.; Masamune, S.; Roush, W.R.; Sakai, T. Tetrahedron Lett. 1984, 25, 2183.

^{417. (}a) Kobayashi, S.; Shimizu, H.; Yamashita, Y.; Ishitani, H.; Kobayashi, H. J. Am. Chem. Soc. 2002, 124, 13678; (b) Yamashita, Y.; Kobayashi, S. J. Am. Chem. Soc. 2004, 126, 11279.



Apart from the nitro compound-phenylisocyanate route, two other procedures are used to prepare nitrile oxides. These two methods are (*1*) treatment of a hydroxamic acid with base and (*2*) oxidation of substituted oximes.⁴¹⁸ Nitrolic acids [R(NO₂)C=NOH] also give nitrile oxides upon heating.⁴¹⁹ Relatively complex applications of this reaction are possible.^{420,421} A [3+2]-cycloaddition reaction of nitrile oxide was catalyzed by antibodies.⁴²² Nitrile oxide cycloadditions have also been done in supercritical carbon dioxide as the reaction medium.⁴²³

The nitrile oxide disconnection is



11.12.D. Nitrones



Nitrones (470) are potent dipoles in cycloaddition reactions.⁴²⁴ Cycloaddition of an alkene to a nitrone produces an isoxazolidine (471), and internal cycloaddition gives a fused-ring isoxazolidine (472 \rightarrow

473). Nitrones are commonlyprepared

in situ via oxidation of an *N*-alkenyl hydroxylamine or condensation of an aldehyde with *N*-methyl hydroxylamine

$ \begin{array}{c} \stackrel{-O}{\underset{R^{1}}{\overset{+}{}}} \\ R^{1} \\ 472 \end{array} \qquad \qquad$

^{418.} Grundmann, C.; Grünanger, P. The Nitrile Oxides, Springer-Verlag, Berlin, 1971.

^{419.} Matt, C.; Gissot, A.; Wagner, A.; Mioskowski, C. Tetrahedron Lett. 2000, 41, 1191.

^{420.} See Tufariello, J.J. Acc. Chem. Res. 1979, 12, 396.

^{421. (}a) Cornforth, J.W. in Jackson, A.H.; Smith, K.M. *The Total Synthesis of Natural Products, Vol 1*, ApSimon, J. (Ed.), Wiley, New York, *1973*, p.143; (b) Traverso, G.; Barco, A.; Pollini, G.P.; Anastasia M.; Sticchi, V.; Pirillo, D. *Il Farmaco Ed. Sci. 1969*, *24*, 946 [*Chem. Abstr. 72*: 78342u, *1970*].

^{422.} Toker, J.D.; Wentworth Jr., P.; Hu, Y.; Houk, K.N.; Janda, K.D. J. Am. Chem. Soc. 2000, 122, 3244.

^{423.} Lee, C.K. Y; Holmes, A.B.; Al-Duri, B.; Leeke, G.A.; Santos, R.C.D.; Seville, J.P.K. Chem. Commun. 2004, 2622.

^{424.} See reference 65, pp 777-778.

or any secondary hydroxylamine.⁴⁰⁴ The HOMO_{nitrone}-LUMO_{alkene} ΔE also suggests that nitrones react best with electron-deficient alkenes (such as methyl acrylate) The HOMO coefficients for 474 (Table 11.13) and the LUMO coefficients of methyl acrylate (Table 11.1) suggests

that the electron-withdrawing substituent is aligned with the C terminus of the dipole, giving regioisomer **475**. When a nitrone reacts with a simple alkene such as propene (see Table 11.1), the same regiochemical

$$\begin{bmatrix} H_{.+},O^{-}_{0.74} \\ H_{.}^{-0.65} \\ H_{.}^{-0.65} \end{bmatrix} + \bigcup_{0.47}^{0.69} CO_{2}Me \xrightarrow{H_{.},O}_{CO_{2}Me} CO_{2}Me$$

outcome is predicted. The small difference in the magnitudes of the orbitals suggests poor regioselectivity, but this is not always the case and the presence of an electron-withdrawing group leads to good regioselectivity. There is a report in which nitrones react with phenyl alkynes to give β -lactams.⁴²⁵ In a synthesis of stemonidine,⁴²⁶ Figueredo and coworkers reacted nitrone **476** and a conjugated ester to give a 78% yield of **477** along with 5% of the diastereomer. Nagasawa and co-workers used an alkene without an electron-withdrawing substituent in a synthesis of crambescidin 359.⁴²⁷ Nitrone **478** reacted with alkene **479** in refluxing toluene to give a 67% yield of the desired stereoisomer **480**, again with good regioselectivity.



Alkyl dipolarophiles with a tendency for strong secondary orbital interactions give significant amounts of the endo product.⁴²⁸ Racemization can occur in the cycloadduct after it is formed in some cases.⁴²⁹ Sibi and co-workers developed a chiral catalyst that leads to *exo*-selectivity in nitrone cycloaddition reactions.⁴³⁰ Reaction of **481** with the nitrone shown, catalyzed by the copper triflate-bis(oxazolidine) complex **482**, gave a 94% yield of **483** (96:4 *exo:endo*) and in 98% ee for the *exo* product shown.

^{425.} Ye, M.-C.; Zhou, J.; Tang, Y. J. Org. Chem 2006, 71, 3576.

^{426.} Sanchez-Izquierdo, F.; Blanco, P.; Busque, F.; Alibes, R.; de March, P.; Figueredo, M.; Font, J.; Parella, T. Org. Lett. 2007, 9, 1769.

^{427.} Nagasawa, K.; Georgieva, A.; Koshino, H.; Nakata, T.; Kita, T.; Hashimoto, Y. Org. Lett. 2002, 4, 177.

^{428.} Tufariello, J.J.; Ali, Sk.A. Tetrahedron Lett. 1978, 4647.

^{429.} Boyle, L.W.; Peagram, M.J.; Whitham, G.H. J. Chem. Soc. B 1971, 1728.

^{430.} Sibi, M.P.; Ma, Z.; Jasperse, C.P. J. Am. Chem. Soc. 2004,126, 718.



Nitrones can be prepared by reaction of an aldehyde or ketone and a *N*-alkylhydroxylamine, as in the reaction of ketone **484** with hydroxylamine **485** to give nitrone **486**. Treatment with ethyl acrylate resulted in a 9:1 mixture of isoxazolidine (**487**) as well as a diastereomer in 74% yield, as part of the Snider and Lin synthesis of (–)-FR901483.⁴³¹ An alternative preparation of nitrones⁴³² is via reduction of a nitro-ketone with zinc, which gave the nitrone *in situ*. Intramolecular cycloadditions are possible with nitrones, giving the expected cycloadduct.⁴³³ If C2 of the alkene and the α -position of the nitrone were hindered, however, a bridged-bicyclo[3.2.1] product was produced in significant amounts.⁴³³ In a synthesis of neplanocin A by Gallos and co-workers,⁴³⁴ reaction of ketone **488** and MeNHOH in the presence of pyridine led to nitrone **489**. Subsequent heating initiated the intramolecular cycloaddition that gave **490** in 75% overall yield from **488**. Enantioselective nitrone cycloaddition reactions have been reported, using chiral imidazolidinones^{435a} or chiral aluminum BINOL complexes.^{435b} Examples of enantioselective cycloadditions were given in a review.⁴³⁶



- 431. Snider, B.B.; Lin, H. J. Am. Chem. Soc. 1999, 121, 7778.
- (a) Tufariello, J.J.; Trybulski, E.J. J. Org. Chem. 1974, 39, 3378; (b) Gössinger, E.; Imhof, R.; Wherli, H. Helv. Chim. Acta 1975, 58, 96.
- 433. (a) LeBel, N.A. Trans. N.Y. Acad. Sci. 1965, 27, 858 [Chem. Abstr. 64:548h 1966]; (b) Reference 404, p 124; (c) LeBel, N.A.; Whang, J.J. J. Am. Chem. Soc. 1959, 81, 6334.
- 434. Gallos, J.K.; Stathakis, C.I.; Kotoulas, S.S.; Koumbis, A.E. J. Org. Chem. 2005, 70, 6884.
- 435. (a) Jen, W.S.; Wiesner, J.J.M.; MacMillan, D.W.C. J. Am. Chem. Soc. 2000, 122, 9874; (b) Jensen, K.B.; Roberson, M.; Jørgensen, K.A. J. Org. Chem. 2000, 65, 9080.
- 436. Gothelf, K.V.; Jørgensen, K.A. Chem. Commun. 2000, 1449.

The nitrone disconnection is



11.12.E. Diazoalkanes



Diazoalkanes are common 1,3-dipoles used in organic synthesis (see sec. 13.9.C for other reactions of diazoalkanes). As diagrammed in Figure 11.21, diazomethane should react fastest with electron deficient alkene (C=C–Z) and slowest with electron-rich alkenes (C=C–X). Orbital coefficients indicate the regiochemical preferences as shown

in **491** and **492** for various alkenes. A synthetic example is the [3+2]-cycloaddition of vinyl diazoalkane **493** with the terminal alkene moiety of (1,3,5Z)-octatriene, to give pyrazoline **494** in 55% yield.⁴³⁷ Photolysis (sec. 11.10.B) of the pyrazoline led to extrusion of molecular nitrogen (N₂) via a nonsynchronous cleavage of the C–N bond.⁴³⁸ This reaction is thought to proceed via discreet diradical intermediates⁴³⁹ that close to form a cyclopropane ring.⁴⁴⁰ In this example, photolysis of **494** gave a mixture of **495** and **496**. Cyclopropane **496** was isolated and then converted to ectocarpene via a Cope rearrangement (sec. 11.12.C). The synthetic utility of the pyrazoline product arises from the extrusion of nitrogen from the molecule under relatively mild conditions.



Figure 11.21. Reactivity of diazomethane with alkenes. [Reprinted with permission from Houk, K.N.; Sims, J.; Watts, C.R.; Luskus, L.J. J. Am. Chem. Soc. 1973, 95, 7301. Copyright © 1973 American Chemical Society.]



^{437.} Schneider, M.P.; Goldbach, M. J. Am. Chem. Soc. 1980, 102, 6114.

^{438.} Hiberty, P.C.; Jean, Y. J. Am. Chem. Soc. 1979, 101, 2538.

^{439.} Givens, R.S.; Oettle, W.F. J. Am. Chem. Soc. 1971, 93, 3301.

^{440.} See reference 65, pp 137-139.

The reaction is amenable to intramolecular [3+2]-cycloadditions.⁴⁴¹ There are application in which extrusion of nitrogen is not a desirable pathway. In a synthesis of manzacidin A by Maruoka and co-workers, [3+2]-cycloaddition of ethyl diazoacetate to methacrolein (**497**) gave pyrazoline **498** in 54% yield and 90% ee.⁴⁴² Subsequent reduction of the aldehyde with sodium borohydride and treatment with trimethyl orthoformate and tosic acid led to **499**, a key intermediate in the synthesis. Later in the synthesis, the pyrazoline unit was reduced to a 1,3-diamine and the [3+2]-cycloaddition was used to set the 1,3-diamine subunit.



A general diazoalkane disconnection is



11.12.F. Azomethine Ylids

Azomethine ylids are useful for the synthesis of pyrrolidine-containing compounds. Table 11.13 indicated electron-deficient alkenes and simple alkenes react fastest (in that order), but the orbital coefficients for the simple case predicts near symmetrical orbital density with simple azomethine ylids (see **500**) and little regioselectivity in the cyclic imine products. Reaction of **500** with methyl acrylate is therefore expected to give a mixture of pyrrolidines **501** and **502** and reaction with propene would also lead to a mixture of regioisomers. Clearly, substituents at either carbon or on the nitrogen will influence the regioselectivity. An alkyl group attached to the imino carbon leads to formation of different reactive dipoles, including **503a** and its resonance contributor **503b**. The presence of the electron-releasing alkyl group will change the orbital coefficients, leading to some regioselectivity in the cycloaddition. The relative stability of the iminium salt moiety (C=NR₂⁺) will also play a role. Resonance contributor **503b**, and is expected to dominate the cycloaddition.



^{441.} Piers, E.; Geraghty, M.B.; Soucy, M. Synth. Commun. 1973, 3, 401.

^{442.} Kano, T.; Hashimoto, T.; Maruoka, K. J. Am. Chem. Soc. 2006, 128, 2174.

The two resonance forms in azomethine ylids lead to formation of a mixture of regioisomeric cycloadducts in reactions with alkenes. Resonance stabilizing substituents usually enhance the regioselectivity, and intramolecular reactions generally favor only one mode of addition. An example of an intermolecular reaction is taken from a synthesis of (–)-kainic acid by Fukuyama and co-workers,⁴⁴³ in which conjugated lactone (**504**) reacted with azomethine ylid **505** (generated *in situ* from **506** and trifluoroacetic acid) to give **507** in 83% yield and a diastereoselectivity of 20:1.



Intramolecular versions of the reaction form polycyclic systems. In a synthesis of pancracine by Pandey and co-workers,⁴⁴⁴ silylmethylamine **508** was treated with 2.5 equivalents of silver fluoride to generate the azomethine ylid **509**, which cyclized to give **510** in 56% yield as a single diastereomer.



The azomethine ylid disconnection is



11.12.G. Azomethine Imines

[3+2]-Dipolar additions of azomethine imines (see **511**) and alkenes give tetrahydropyrazines (pyrazolizidines) such as **512**. In this example, reaction with methyl acrylate is predicted to give the regioisomer with the carbomethoxy group adjacent to the nitrogen. A similar regiochemical preference is predicted upon reaction with simple alkenes such as propene. Azomethine imines are usually generated from substituted hydrazone derivatives, which are prepared by reaction of the corresponding aldehydes or ketones with substituted hydrazine

^{443.} Morita, Y.; Tokuyama, H.; Fukuyama, T. Org. Lett. 2005, 7, 4337.

^{444.} Pandey, G.; Banerjee, P.; Kumar, R.; Puranik, V.G. Org. Lett. 2005, 7, 3713.

derivatives.⁴⁴⁵ Overman and co-workers used an intramolecular 1,3-dipolar cycloaddition of azomethine imines to prepare triazacyclopenta[cd]pentalenes.⁴⁴⁶ When **513** was treated with thiosemicarbazide, initial formation of **514** was followed by formation of the azomethine imine *in situ*, and cycloaddition gave an 89% yield of **515**. Note that the carboethoxy unit in **514** was converted to an amide unit during the course of the reaction.



The azomethine imine disconnection is

11.12.H Alkyl Azides

Alkyl azides have the structure $R-N_3$ ($R-N^--^+N=N$) and undergo [3+2]-cycloaddition reactions. The first report of the reaction of an azide with an alkene was by Wolff in 1912,⁴⁴⁷ and its scope and stereochemistry were later examined by Alder and Stein.⁴⁴⁸ This [3+2]-cycloaddition reaction is believed to be concerted⁴⁴⁹ and it gives a triazoline product such as **516**. In Table 11.13, hydrazoic acid (HN₃) was shown to have a HOMO of -11.5 eV, with orbital



coefficients of 1.56 and 0.72. In a reaction with methyl acrylate, the [3+2]-cycloadduct is triazoline **516**, based on correlation of the largest orbital coefficients. This heterocycle usually decomposes thermally to give pyrroline derivatives,⁴⁵⁰ and photochemically to give

- 449. Scheiner, P.; Schomaker, J.H.; Deming, S.; Libbey, W.J.; Nowack, G.P. J. Am. Chem. Soc. 1965, 87, 306.
- 450. Logothetis, A.L. J. Am. Chem. Soc. 1965, 87, 749.

^{445. (}a) Oppolzer, W. Tetrahedron Lett. 1970, 2199; (b) Idem Ibid. 1972, 1707.

^{446.} Bélanger, G.; Hong, F.-T. Overman, L.E.; Rogers, B.N. Tellew, J.E.; Trenkle 1, W.C. J. Org. Chem. 2002, 67, 7880.

^{447.} Wolff, L. Annalen 1912, 394, 23, 59, 68.

^{448. (}a) Alder, K.; Stein, G. Annalen 1931, 485, 211; (b) Idem Ibid. 1933, 501, 1.

aziridines.^{451,452} An example, taken from Marazano and co-workers' synthesis of the ABC ring of manzamine A,⁴⁵³ reacted mesylate **517** with sodium azide in hot DMF to give **518**. The [3+2]-cycloaddition produced triazole **519**, which extruded nitrogen to give **520**. In this example, proton transfer occurred to give **521** along with **522** (resulting from epimerization of the proton adjacent to the ester unit) in a 3:2 ratio, in 67% combined yield.⁴⁵³ Photochemical decomposition of the triazoline gives the aziridine⁴⁵² but pyrrolines can also be formed.^{412a} An aziridine is not necessarily an intermediate in the pathway that forms five-membered ring derivatives, however.⁴⁵⁴



An interesting synthetic application of this process is Hudlicky and co-worker's preparation of several pyrrolizidine alkaloids, via treatment of conjugated ketone **523** with sodium azide (NaN₃) to give keto-azide **524** in 88% yield.⁴⁵⁵ Addition of the **524** to the diene apparently generated a triazoline, which was not isolated but decomposed to a transient vinyl aziridine.⁴⁵⁶ Reduction of the carbonyl unit in **524** to give alcohol **525** (in 64% yield) used cerium borohydride (NaBH₄/CeCl₃, sec. 4.4.B). Subsequent heating in toluene gave **526** and **527** in about 50% yield (as a 64:36 mixture) via cycloaddition followed by extrusion of nitrogen (N=N).⁴⁵⁵ Hudlicky combined this reaction with a nitrogen analog of the vinyl cyclopropane rearrangement (to be discussed in sec. 11.12.B). Flash vacuum pyrolysis of **526** induced the rearrangement to give pyrrolizidine **528** in 43% yield (after hydrogenation of the initially formed unstable enamine). The extent of nitrogen extrusion to form an aziridine ring depended on the reaction

- 454. Leeson, P.D.; Carling, R.W.; James, K.; Baker, R. J. Org. Chem. 1990, 55, 2103.
- 455. Hudlicky, T.; Seoane, G.; Lovelace, T.C. J. Org. Chem. 1988, 53, 2094.
- 456. Hudlicky, T.; Frazier, J.O.; Kwart, L.D. Tetrahedron Lett. 1985, 26, 3523.

^{451. (}a) Scheiner, P. J. Am. Chem. Soc. 1968, 90, 988; (b) Huisgen, L.; Möbius, G.; Müller, H.; Stangl, G.; Szeimies, G.; Vernon, J.M. Chem. Ber. 1965, 98, 3992.

^{452.} See reference 65, p 819.

^{453.} Herdemann, M.; Al-Nourabit, A.; Martin, M.-T.; Marazano, C. J. Org. Chem. 2002, 67, 1890.

conditions.⁴⁵⁷ Alkyl azides of the type shown in these examples can be generated by reaction of a suitable derivative with tosyl azide⁴⁵⁸ or mesyl azide.⁴⁵⁹



The alkyl azide disconnection is:



11.12.1. Carbonyl Ylids



The final class of dipoles discussed here are the carbonyl ylids. Padwa et al. generated these reactive intermediates from a rhodium (II)-catalyzed reaction with 1-diazopentanediones.⁴⁶⁰ A synthetic example of this reaction is the formation of carbonyl ylid **530** from diazoketone **529** upon treatment with dirhodium tetraacetate, taken from Schmalz and co-worker's synthesis of (–)-colchicine.⁴⁶¹ Once **530** was generated, an intramolecular [3+2]-cycloaddition gave **531** in 64% yield and >98% de. Note that in cases reported by Padwa,^{460a} rhodium catalysts other than

- 457. Hudlicky, T.; Frazier, J.O.; Seoane, G.; Tiedje, M.; Seoane, A.; Kwart, L.D.; Beal, C. J. Am. Chem. Soc. 1986, 108, 3755.
- 458. (a) Ledon, H.T. Org. Synth. Coll. Vol. 6 1988, 414; (b) Hudlicky, T.; Govidan, S.V.; Frazier, J.O. J. Org. Chem. 1985, 50, 4166.
- (a) Taber, D.F.; Ruckle Jr., R.E.; Hennessy, M.J. J. Org. Chem. 1986, 51, 4077; (b) Boyer, J.H.; Mack, C.H.; Goebel, W.; Morgan Jr., L.R. Ibid. 1959, 23, 1051.
- (a) Padwa, A.; Carter, S.P.; Nimmesgern, H. J. Org. Chem. 1986, 51, 1157; (b) Padwa, A.; Carter, S.P.; Nimmesgern, H.; Stull, P.D. J. Am. Chem. Soc. 1988, 110, 2894; (c) Padwa, A.; Fryxell, G.E.; Zhi, L. J. Org. Chem. 1988, 53, 2875; (d) Idem J. Am. Chem. Soc. 1990, 112, 3100.
- 461. Graening, T.; Bette, V.; Neudorfl, J.; Lex, J.; Schmalz, H.-G. Org. Lett. 2005, 7, 4317.

 $Rh_2(OAc)_4$ were required to generate the carbonyl ylid.

11.13. SIGMATROPIC REARRANGEMENTS

11.13.A. [m, n]-Sigmatropic Shifts



Fleming defines a sigmatropic rearrangement as a "reaction in which a σ bond (a substituent) moves across a conjugated system to a new site", as in the transfer of hydrogen across the face of **532a** to generate **532b** (which in this simple case is identical to **532a**)⁴⁶² The nomenclature used for this process

is a [m,n]-sigmatropic shift, where an atom or group migrates from position *m* to position *n*. The shift for **532** moves the hydrogen atom at bond 1 to bond 5, a [1,5]-sigmatropic shift. "A [1,5] sigmatropic hydrogen-transfer process must possess a six-membered pericyclic transition state in accordance with the requirements of orbital symmetry conservation".⁴⁶³ The migrating group is hydrogen in 532, but carbon and other atoms or groups can migrate. Migration can occur from the same face of the π -system or the opposite face, as illustrated in Figure 11.22.⁴⁶⁴ Migration from C1 to C5 across the top face of the molecule as drawn is called a suprafacial [1,5] hydrogen shift. In other words, an atom moves from C1, across the π -face of **532**, and forms a new bond to C5 on the same face. "The σ bond is made and broken on the same side of the conjugated system".^{465,462} Another possibility is the antarafacial [1,5] shift also shown in Figure 11.22, where the atom moves from C1, but attaches to C5 on the opposite (bottom) face of **532**. While the antarafacial shift is an inversion, it does not cause inversion of the geometry of a single atom, but rather moves the migrating group to the opposite face.⁴⁶¹ A synthetic example heated allene 533 to 100°C, which led to formation of 534 in 59% yield.⁴⁶⁶ This transformation was essential to Okamura and co-worker's synthesis of 9,11-dehydrovitamin D₃ analogs.



^{462.} Reference 7, p 98.

- 465. Roth, W.R.; König, J.; Stein, K. Chem. Ber. 1970, 103, 426.
- 466. Okamura, W.H.; Aurrecoechea, J.M.; Gibbs, R.A.; Norman, A.W. J. Org. Chem. 1989, 54, 4072.

^{463.} Kwart, H.; Brechbiel, M.W.; Acheson, R.M.; Ward, D.C. J. Am. Chem. Soc. 1982, 104, 4671.

^{464.} Miller, B. Advanced Organic Chemistry: Reactions and Mechanisms, 2nd Ed., Pearson/Prentice Hall, Upper Saddle River, NJ, 2004, p. 91.



Figure 11.22. Suprafacial[1,5] and antarafacial [1,5] shifts. [Reprinted with permission from Miller, B. *Advanced Organic Chemistry: Reactions and Mechanisms, 2nd Ed.*, Pearson/Prentice Hall, Upper Saddle River, NJ, 2004, p. 91. Copyright © 2004.]

Sigmatropic shifts do not always require high temperatures. The [1,5]-sigmatropic rearrangement of substituted cyclopentadienes (535) occurs readily at room temperature,⁴⁶⁷ to generate three different species (535-537). Note that the rearrangement produces two forms of 537 (a and b) that are identical when R = H, but with disubstituted cyclopentadienes, may be different isomers. The presence of several isomeric compounds leads to regiochemical control problems in Diels-Alder reactions of substituted cyclopentadienes, as discussed in Section 11.8⁴⁶⁸ (see 219).²⁴⁴ Those rearrangements can now be defined as a series of [1,5]-sigmatropic hydrogen shifts.



It is possible to trap the 5-substituted cyclopentadiene, however, as in the Diels-Alder reaction of **539** to give **540** in 55% yield.⁴⁶⁹ Diene **539** was prepared via alkylation of the thallous salt of cyclopentadienyl anion (**538**). Note that the isolation technique for **539** avoided heating above 0°C, in order to suppress the [1,5]-sigmatropic rearrangement. The Diels-Alder reaction that produced **540** used a Lewis acid to catalyze the reaction, allowing the temperature to be

^{467.} Alder, K.; Ache, H.-J. Chem. Ber. 1962, 95, 503.

^{468.} Unpublished results, cited as reference 22 in Oppolzer, W. Angew. Chem. Int. Ed. 1977, 16, 10, see p 13.

 ^{469. (}a) Corey, E.J.; Ravindranathan, T.; Terashima, S. J. Am. Chem. Soc. 1971, 93, 4326; (b) Corey, E.J.; Keolliker, U.; Neuffer, J. Ibid. 1971, 93, 1489.

maintained below 0°C.469

Migration of carbon atoms around 1,3,5-cycloheptatrienes (tropilidenes) is a sigmatropic rearrangement involving an electrocyclization to a norcaradiene, followed by 1,5-shifts of a cyclopropane bond. When **541**, **542**, or **543** are heated to >300°C, the methyl group appears to "walk" around the ring, and this rearrangement is called the "walk rearrangement".⁴⁷⁰ Initial electrocyclization to **544** was followed by sequential 1,5-shifts-electrocyclizations. It is noted that **545** and **546** are isolated, and since they result from a hydrogen shift but there is no cyclization an alternative mechanism is possible.^{470a,471}



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Sigmatropic rearrangements can occur in other π systems. In an allylic system, hydrogen migration requires an antarafacial shift for a [1,3]-sigmatropic rearrangement (see **547**),⁴⁷² and the reaction is rare.⁴⁷³ With longer conjugated systems such as 1,3,5-heptatriene, [1,7]-sigmatropic rearrangement is thermally allowed, although it is an antarafacial shift⁴⁷⁴ (see **548**). The longer carbon backbone can twist, which allows antarafacial delivery of the C1 hydrogen to C7, as shown. This rearrangement can be difficult, and rarely occurs in cyclic trienes. There are exceptions, however, as in quinol **549** where heating in benzene led to **550**,

^{470. (}a) Berson, J.A. Accs. Chem. Res. **1968**, 1, 152; (b) Berson, J.A.; Willcott III, M.R. J. Am. Chem. Soc. **1966**, 88, 2494.

^{471. (}a) Ter Borg, A.P.; Razenberg, E.; Kloosterziel, H. Rec. Trav. Chim., 1965, 84, 1230; (b) Egger, K.W. J. Am. Chem. Soc. 1967, 89, 3688.

^{472.} Miller, B. Advanced Organic Chemistry: Reactions and Mechanisms, 2nd Ed., Pearson/Prentice Hall, Upper Saddle River, NJ, 2004, p. 94.

^{473.} Baldwin, J.E.; Fleming, R.H. J. Am. Chem. Soc. 1972, 94, 2140.

^{474.} Näf, F.; Decorzant, R.; Thommen, W.; Willhalm, B.; Ohloff, G. Helv. Chim. Acta 1975, 58, 1016.

and a subsequent [1,7]-H shift gave trihydroxybenzene **551** as part of Nicolaou and coworker's synthesis of bisorbicillinoids.⁴⁷⁵



[Reprinted with permission from Miller, B. Advanced Organic Chemistry: Reactions and Mechanisms, 2nd Ed., Pearson/Prentice Hall, Upper saddle River, NJ, 2004, p. 94. Copyright © 2004.]



11.13.B. Vinylcyclopropane Rearrangements



Cyclopropylcarbinyl systems generates cyclopentenes via a [1,3]-alkyl sigmatropic rearrangement.⁴⁷⁶ Vigorous heating of vinyl cyclopropane **552** (usually >500°C) gives rearrangement to a cyclopentene, as shown. The first reports of this rearrangement were by Vogel⁴⁷⁷ and

by Overberger and Borchert.⁴⁷⁸ Both concerted⁴⁷⁹ and diradical⁴⁸⁰ pathways have been proposed for this reaction. An alternative proposal suggests a continuous diradical transition state.⁴⁸¹ A

^{475.} Nicolaou, K.C.; Vassilikogiannakis, G.; Simonsen, K.B.; Baran, P.S.; Zhong, Y.-L.; Vidali, V.P.; Pitsinos, E.N.; Couladouros, E.A. J. Am. Chem. Soc. 2000, 122, 3071.

^{476. (}a) Baldwin, J.E. Chem. Rev. 2003, 103, 1197; (b) Mil'vitskaya, E.M.; Tarakanova, A.V.; Plate, A.F. Russ. Chem. Rev. 1976, 45, 469; (c) Frey, H.M. Adv. Phys. Org. Chem. 1966, 4, 147 (see pp 155-163 and 175-176).
477. Viscol E. A. Chem. 10(0, 72) 4.

^{477.} Vogel, E. Angew. Chem. 1960, 72, 4.

^{478.} Overberger, C. G.; Borchert, A. E. J. Am. Chem. Soc. 1960, 82, 1007.

 ⁽a) Shields, T.C.; Billups, W.E.; Lepley, A.R. J. Am. Chem. Soc. 1968, 90, 4749; (b) Berson, J.A.; Dervan, P.B.; Malherbe, R.; Jenkins, J.A. Ibid. 1976, 98, 5937; (c) Gajewski, J.J.; Olson, L.P. Ibid. 1991, 113, 7432.

^{480. (}a)Willcott, M.R.; Cargle, R.L. J. Am. Chem. Soc. 1967, 89, 723; (b)Doering, W.von E.; Schmidt, D. Tetrahedron 1971, 27, 2005; (c)Roth, W.R.; Schmidt, E.K.G. Tetrahedron Lett. 1971, 3639; (d)Zimmerman, H.E.; Fleming, S.A.J. Am. Chem. Soc. 1983, 105, 622; (e) McGaffin, G.; de Meijere, A.; Walsh, R. Chem. Ber. 1991, 124, 939.

 ⁽a) Doering, W. von E.; Sachdev, K. J. Am. Chem. Soc. 1974, 96, 1168; (b) Idem Ibid. 1975, 97, 5512; (c) Roth,
 W.R.; Lennartz, H.; Doering, W. von E.; Birladeanu, L.; Guyton, C.A.; Kitagawa, T. Ibid. 1990, 112, 1722.

synthetic example is Trost and Parquette's synthesis of 11-hydroxyjasionone,⁴⁸² where **553** was heated to 600°C at 0.06 mmHg (FVP) to give a 97% yield of **554**.



A useful source of vinylcyclopropane derivatives is the cyclopropanation reaction that occurs when diazoalkanes are decomposed to form a carbene-type intermediate in the presence of a diene (sec. 13.9.C.i). Heating diazoketone **555** in the presence of a cupric salt generates a carbene, which added to one C=C unit of the diene moiety to give the bicyclo[3.1.0]hexanone derivative **556**. Heating to 580°C induced the vinylcyclopropane rearrangement, which gave a cyclopentene ring in **557**. Hudlicky et al. converted **557** to hirsutene (**558**) in two steps.⁴⁸³ Additional examples of cyclopropanation of alkenes with diazoalkane derivatives will be discussed in sections 13.9.B.ii and 13.9.C. This vinylcyclopropane rearrangement is general in its scope, and very useful in organic synthesis.⁴⁸⁴ There is a distinct preference for the trans isomer, as seen in the conversion of **555** to **556**, where one cyclopropyl hydrogen and the methyl have a trans-relationship.⁴⁸⁵



The vinylcyclopropane rearrangement is key step in Trost's **seco-alkylation** sequence (see sec. 8.8.B.ii). In this protocol, trimethylsilyloxyvinylcyclopropanes such as **559** are generated by reaction with diphenylcyclopropyl sulfide, and then with lithium diisopropyl amide (LDA). These steps open the oxaspiropentane, and the resulting alkoxide anion is trapped with chlorotrimethylsilane. Thermal rearrangement of the vinylcyclopropane^{486bc} gave the five-membered ring silyl enol ether (**560**), which gave ketone **561** upon hydrolysis.^{486a}

^{482.} Trost, B.M.; Parquette, J.R. J. Org. Chem. 1994, 59, 7568.

^{483.} Hudlicky, T.; Kutchan, T.M.; Wilson, S.R.; Mao, D.T. J. Am. Chem. Soc. 1980, 102, 6351.

^{484.} For another synthetic example, see Wender, P.A.; Eissenstat, M.A.; Filosa, M.P. J. Am. Chem. Soc. 1979, 101, 2196.

^{485.} For another synthetic example, see Marino, J.P.; Kaneko, T. J. Org. Chem. 1974, 39, 3175.

 ^{486. (}a) Trost, B.M.; Bogdanowicz, M.J. J. Am. Chem. Soc. 1973, 95, 289; (b) Wilcott, M.R.; Cargle, V.H. Ibid. 1967, 89, 723; (c) Idem Ibid. 1969, 91, 4310.



The sigmatropic hydrogen shift and vinylcyclopropane disconnections are



11.13.C. [2.3]-Sigmatropic Rearrangement (Wittig Rearrangement)

Other [m,n]-signatropic rearrangements are known. An important rearrangement that is useful in synthesis is the [2.3]-signatropic rearrangement known as the Wittig rearrangement.



11.13.C.i. Wittig Rearrangement. Heating sulfur ylids (sec. 8.8.B) bearing an allylic group converts them to unsaturated sulfides⁴⁸⁷ via a concerted [2,3] sigmatropic rearrangement.⁴⁸⁸ Nitrogen ylids⁴⁸⁹ give similar rearrangements, as do the conjugate bases of allylic ethers (**563**). This latter rearrangement involves treatment of an allylic ether (**562**) with a suitable base to give the anion (**563**), which undergoes a [2,3]-sigmatropic rearrangement to give the homoallylic alcohol **564**. This transformation is known as the **[2,3]-Wittig rearrangement.**⁴⁹⁰ It is noted that the [2,3]-Wittig rearrangement may involve severe deformation of the molecule in order to

^{487.} For example, see (a) Blackburn, G.M.; Ollis, W.D.; Plackett, J.D.; Smith, C.; Sutherland, I.O. *Chem. Commun.* 1968, 186; (b) Trost, B.M.; LaRochelle, R. *Tetrahedron Lett.* 1968, 9, 3327; (c) Kirmse, W.; Kapps, M. *Chem. Ber.* 1968, 101, 994, 1004; (d) Ceré, V.; Paolucci, C.; Pollicino, S.; Sandri, E.; Fava, A. J. Org. *Chem.* 1981, 46, 3315; (e) For a review as applied to ring expansions, see Vedejs, E. Acc. Chem. Res. 1984, 17, 358.
488. Haffmann, P.W. Angrun, Chem. Int. Ed. 1970, 18, 562.

^{488.} Hoffmann, R.W. Angew. Chem. Int. Ed. 1979, 18, 563.

^{489. (}a) Jemison, R.W.; Ollis, W.D. J. Chem. Soc., D: Chem. Commun. 1969, 294; (b) Honda, K.; Inoue, S.; Sato, K. J. Am. Chem. Soc. 1990, 112, 1999.

⁽a) Cast, J.; Stevens, T. S.; Holmes, J. J. Chem. Soc. 1960, 3521; (b) Makisumi, Y.; Notzumoto, S. Tetrahedron Lett. 1966, 7, 6393; (c) Nakai, T.; Mikami, K. Org. React. 1994, 46, 105; (d) Marshall, J.A. Comp. Org. Synth. 1991, 3, 975; (e) Nakai, T.; Mikami, K. Chem. Rev. 1986, 86, 885; (f) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-102; (g) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 700-701.

proceed.⁴⁹¹ It has been shown that SmI₂ induces a [2,3] Wittig rearrangement.⁴⁹²

Enantioselective [2,3]-Wittig rearrangements have been reported. The product of this reaction has potential stereogenic centers at C-3 and C-4 (if $R^5 \neq R^6$), and if the starting ether is optically active because of a stereogenic center at C-1 the product may be optically active as well. Many examples are known in which an optically active ether was converted to a product that was optically active, because of chirality at C-3, C-4 or both.⁴⁹³ If a suitable stereogenic center is present in R¹ (or if a functional group in R¹ made to incorporate a stereogenic center), then stereocontrol over three contiguous stereogenic centers can be achieved. Stereocontrol of the new double bond (*E* or *Z*) has also been accomplished.



A synthetic example of the [2,3]-Wittig rearrangement is taken from Martin and co-worker's synthesis of (+)-ambruticin S.^{494,495} In this synthesis, the OH unit in alcohol **565** was *O*-alkylated with trimethyltin iodomethane to give **566**. Subsequent reaction with butyllithium led to formation of the anion and rapid Wittig rearrangement to give alcohol **567** in 70% overall yield after workup, with high diastereoselectivity (>10:1). A second example, taken from Tsubuki, Takahashi and Honda's synthesis of one unit of kallolide A,⁴⁹⁶ illustrates a useful intramolecular variation of the Wittig rearrangement, where stereocontrol in the product was a function of the stereochemistry of the alkene unit in the starting allylic ether. Treatment of *E*-**568** with *sec*-butyllithium generated a 95:5 mixture of **569** and **570**, in 73% yield, via the [2,3]-Wittig rearrangement. Similar treatment of *Z*-**568** with *sec*-butyllithium, however, gave

491. You, Z.; Koreeda, M. Tetrahedron Lett. 1993, 34, 2597.

- 493. (a) Mikami, K.; Nakai, T. Synthesis 1991, 594; (b) Fujimoto, K.; Nakai, T. Tetrahedron Lett. 1994, 35, 5019;
 (c) Kusche, A.; Brückner, R.; Harms, K. Chem. Ber. 1990, 123, 917; (d) Wu, Y.; Houk, K.N.; Marshall, J.A.
 J. Org. Chem. 1990, 55, 1421; (e) Marshall, J.A.; Wang, X.J. J. Org. Chem. 1990, 55, 2995.
- 494. Kirkland, T.A.; Colucci, J.; Geraci, L.S.; Marx, M.A.; Schneider, M.; Kaelin Jr., D.E.; Martin, S.F. J. Am. Chem. Soc. 2001, 123, 12432.
- 495. Also see Davidson, A.H.; Wallace, I.H. J. Chem. Soc. Chem. Commun. 1986, 1759.
- 496. Tsubuki, M.; Takahashi, K.; Honda, T. J. Org. Chem. 2003, 68, 10183.

^{492. (}a) Kunishima, M.; Hioki, K.; Kono, K.; Kato, A.; Tani, S. J. Org. Chem. 1997, 62, 7542. Also see (b) Hioki, K.; Kono, K.; Tani, S.; Kunishima, M. Tetrahedron Lett. 1998, 39, 5229.

a 5:95 mixture of 569:570 in 84% yield.

Other [2,3] signatropic rearrangements are known. In chapter 8 (sec. 8.6.A) the **Mislow-Evans rearrangement** involved a rearrangement of allylic sulfoxides to allylic alcohols by treatment with a thiophilic reagent such as trimethyl phosphite. This migration is from sulfur to oxygen, and [2,3] oxygen-to-sulfur migrations are also known.⁴⁹⁷ The **Sommelet-Hauser rearrangement** (Sec. 8.8.C.ii) is also a [2,3] signatropic rearrangement.

11.13.C.ii. aza-Wittig Rearrangement. An aza-Wittig rearrangement is known that involves nitrogen ylids (sec. 8.8.C).⁴⁹⁸ The rearrangement is fundamentally similar to the other Wittig rearrangements just discussed. Amides are the most common precursor because the ylid derived from amide are somewhat more stable. A synthetic example is taken from Anderson and Whiting and Anderson's synthesis of kainic acid.⁴⁹⁹ The requisite amide is produced by simple alkylation of allylic bromide **571** with the anion of BocNHCH₂CONMe₂ (91% yield of **572**). Subsequent reaction with LDA generated the anion, and [2,3]-sigmatropic rearrangement occurred spontaneously to give **573** in 78% yield.



11.13.D. The Cope Rearrangement

11.13.D.i. The Normal Cope Rearrangement. Sigmatropic rearrangements are not confined to hydrogen shifts occurring within a π framework. Thermolysis of *1,5-dienes* results in a six π -electron reorganization, which is a [3,3]-sigmatropic



rearrangement illustrated by the interconversion of **574** and **575**. This reaction is known as the **Cope rearrangement**⁵⁰⁰ and both the reactivity and selectivity of this reaction can be explained

^{497. (}a) Braverman, S.; Mechoulam, H. Isr. J. Chem. 1967, 5, 71, (b) Braverman, S.; Stabinsky, Y. J. Chem. Soc., D: Chem. Commun. 1967, 270; (c) Rautenstrauch, V. Chem. Commun. 1970, 526; (d) Tamaru, Y.; Nagao, K.; Bando, T.; Yoshida, Z. J. Org. Chem. 1990, 55, 1823.

 ^{498. (}a) Coldham, I. J. Chem. Soc. Perkin Trans. 1 1993, 1275; (b) Anderson, J.C.; Siddons, D.C.; Smith, S.C.; Swarbrick, M.E. J. Chem. Soc. Chem. Commun. 1995, 1835; (c) Ahman, J.; Somfai, P. J. Am. Chem. Soc. 1994, 116, 9781.

^{499.} Anderson, J.C.; Whiting, M. J. Org. Chem. 2003, 68, 6160.

^{500. (}a) Cope, A.C.; Hardy, E.M. J. Am. Chem. Soc. 1940, 62, 441; (b) Rhoads, S.J.; Raulins, N.R. Org. React. 1975, 22, 1; (c) Schröder, G.; Oth, J.F.M.; Merény, R. Angew. Chem. Int. 1965, 4, 752; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-19; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 170-171.

by frontier molecular orbital theory.⁵⁰¹ In practical terms, a 1,5-diene is converted to another 1,5-diene by a reversible signatropic rearrangement.⁵⁰² The reverse-Cope rearrangement is useful in many applications.⁵⁰³ Calculations suggest two transition states for the Cope rearrangements, a chair (**576**) and a boat (**577**).⁵⁰⁴ In **576**, the orbitals of interest are at the termini (C1 and C6) that reacts via a chair-like conformation (**576**), Mechanistic work also suggests that the transition state^{505,504} for the Cope rearrangement is predominantly aromatic in nature. A boat transition state is also possible (**577**), which is close in energy to **576** according to calculations (37.1 kcal mol⁻¹ for the chair versus 47.8 kcal mol⁻¹ for the boat; 155.3 versus 200.1 kJ mol⁻¹), ⁵⁰⁴ which is in reasonable agreement with experimental data.⁵⁰⁶ In other work, the chair transition state was estimated to be 5.7 kcal mol⁻¹ (23.8 kJ mol⁻¹) lower in energy relative to the boat transition state, ⁵⁰⁷ and there is a preference for the chair conformation.⁵⁰⁸ When substituents are present on the molecule, a destabilizing orbital interaction in the boat transition state can lead to the chair transition state being favored. In general terms, ⁵⁰⁸ if the 1,5-diene cannot attain a chair conformation, the Cope rearrangement is often slow and higher reaction temperatures are required.



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It is known that (E,E)-diene **578** rearranges faster than (Z,Z)-diene **580** in the Cope rearrangement.⁵⁰⁷ The (E,E)-diene is more stable than the (E,Z)-diene by about 2 kcal mol⁻¹ (8.37 kJ mol⁻¹), due to the pseudo-





methyl-hydrogen interactions in transition state **581**. These interactions are absent in transition state **579**, which has two pseudo-equatorial methyl groups.⁵⁰⁷ As

- 501. Fukui, K. Accs. Chem. Res. 1971, 4, 57.
- 502. See reference 65, pp 464-465.
- 503. Cooper, N.J.; Knight, D.W. Tetahedron 2004, 60, 243.
- 504. Dewar, M.J.S.; Jie, C. J. Am. Chem. Soc. 1987, 109, 5893.
- 505. Staroverov, V.N.; Davidson, E.R. J. Am. Chem. Soc. 2000, 122, 186.
- 506. (a) von E. Doering, W; Toscano, V.G.; Beasley, G.H. *Tetrahedron* 1971, 27, 299; (b) von E. Doering, W.; Troise, C.A. J. Am. Chem. Soc. 1985, 107, 5739.
- 507. von E. Doering, W.; Roth, W.R. Tetrahedron 1962, 18, 67.
- 508. Shea, K.J.; Stoddard, G.J.; England, W.P.; Haffner, C.D. J. Am. Chem. Soc. 1992, 114, 2635, and references cited therein.
the steric bulk of the substituents on the diene increases, more vigorous reaction conditions (higher temperatures) are required, illustrated by syn-3,4-disubstituted hexadienes such as **582**.⁵⁰⁷ Two chair-like transition states (**583a** and **583b**) are in equilibrium, and each has a pseudoequatorial and a pseudo-axial group, leading to similar energies for each conformation. Cope rearrangement of **583a** gave **584**, the (*E*,*Z*)-diene, but **583b** also gave the (*E*,*Z*)-isomer (**585**). trans-3,4-Disubstituted hexadiene **586**, however, generated **587a** (with two pseudo-equatorial groups) and **587b** (with two pseudo-axial groups).⁵⁰⁷ Since the 1,3-diaxial interaction (R-R) in **587b** will be greater than the analogous interaction (H-H) in **587a**, **587a** will be lower in energy. Conformation **587a** leads to the (*E*,*E*)-isomer **588** and **587b** leads to the (*Z*,*Z*)-isomer **589**. Since **587a** is the lowest energy transition state, the (*E*,*E*)-diene should predominate. These predictions are borne out with the reaction of meso-2,3-dimethyl-1,5-hexadiene (**582**, R = Me), which gave 99.7% of **584** (R = Me) and 0.3% of **585** (R = Me) at 225°C after 6 h. The (*dl*)-isomer (**586**, R = Me) gave 90% of **588**, 10% of the cis-,cis-diene product and <1% of **589** (R = Me).⁵⁰⁷



von E. Doering and Roth⁵⁰⁷ determined that the reaction gave a >300:1 preference for products derived from the chair transition state over the boat transition state, leading to the energy preference of 5.7 kcal mol⁻¹ (23.9 kJ mol⁻¹) for products derived from the chair transition state mentioned above. The influence of the pseudo equatorial versus the pseudo axial groups can be seen in the Cope rearrangement of **590**, also drawn as the pseudo-diequatorial rotamer. Hexadiene **590** gave only the (*E*,*E*)-diene (**591**) rather than **592** when heated to 80°C for 8 h. The diaxial rotamer⁵⁰⁹ would lead to the unobserved (*Z*,*Z*)-isomer (**592**). The obvious implication is a marked conformational preference for the pseudo-diequatorial rotamer (see the conformational drawing of **590**). This compares with the 3-phenyl-4-methyl derivative, which gave a 90% yield of the (*E*,*E*) diene and 10% of the (*Z*,*Z*)-diene.⁵⁰⁹

^{509.} Lutz, R.P.; Bernal, S.; Boggio, R.J.; Harris, R.O.; McNicholas, M.W. J. Am. Chem. Soc. 1971, 93, 3985.



MOLECULAR MODELING: Woodward-Hoffmann Rules

The *Woodward-Hoffmann rules* suggest that if given the choice, an intramolecular rearrangement will prefer a path that allows high-energy molecular orbitals (in particular, the HOMO) to change smoothly from reactants to products rather than an alternative route that leads to a change in sign. Woodward and Hoffmann referred to the former as an "allowed reactions" and the latter as a "forbidden reactions". Sigmatropic rearrangements such as the Cope rearrangement are one example. The Cope rearrangement of 2E, 4Z, 6E-octatriene can either occur via a *disrotatory* motion (terminal double bonds turning toward each other) to give a *cis* diene, or a *conrotatory* motion (terminal double bonds turning away from each other) to give the less crowded *trans* diene. isomer.



The highest-occupied molecular orbitals for conformers of 2*E*,4*Z*,6*E*-octatriene that are "poised" to *cis* and *trans* 1,5-dienes are displayed on screen (left and right, respectively. Describe the difference between the two orbitals. Which if either corresponds to an allowed reaction?

3,4-Disubstituted dienes (such as **590**) undergo Cope rearrangement more easily (at lower temperatures) than the corresponding 1,6-disubstituted dienes (see **578**). Substituents at the C2

and C5 positions, however, have little effect. These observations can best be explained by identifying the Cope rearrangement as an equilibration process (as seen in $583a \rightarrow 583b$). Under the thermal conditions of the reaction, the thermodynamically most



stable diene will accumulate. Heating 3-methyl-1,5-hexadiene (**593**) gave $\sim 60:40$ mixture of **593** and **594**.⁵¹⁰ In this case, the energy difference between **593** and **594** is rather small, and **593** is only slightly favored. The Cope rearrangement is most efficient when the product diene

^{510.} Levy, H.; Cope, A.C. J. Am. Chem. Soc. 1944, 66, 1684.

of the equilibrium is significantly more stable than the starting diene.

Introducing strain into the molecule lowers the activation barrier for the [3,3]-sigmatropic shift, as does introduction of an oxygen atom. The relative rate of each reaction is inversely proportional to the highest activation barrier:⁵¹¹ 33.5 kcal mol⁻¹ (140.2 kJ mol⁻¹) for **595**,⁵¹² 23.1 kcal mol⁻¹ (96.7 kJ mol⁻¹) for **596**,⁵¹³ 19.4 kcal mol⁻¹ (81.2 kJ mol⁻¹) for **597**,⁵¹⁴ and 18.2 kcal mol⁻¹ (76.2 kJ mol⁻¹) for **598**.⁵¹⁵



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When both strain and stereochemical bias are present in the diene, remarkable rate accelerations can be observed. The activation energy for **596** ($\Delta E \sim 23.1$ kcal mol⁻¹, 96.7 kJ mol⁻¹) is lower than that for the trans isomer, **599** ($\Delta E = 34.0$ kcal mol⁻¹, 142.3 kJ mol⁻¹).⁵¹³ Diene **599** cannot assume either a chair



or a boat conformation without distortion of the molecule, making the Cope rearrangement slow. The cis compound can assume either a chair or a boat conformation and will easily undergo the Cope rearrangement. The strain imparted by a cyclobutane ring is seen in the 3,4 bond of the diene (see **596**), but this strain is diminished in the Cope rearrangement product (**600**), which is an eight-membered ring with some inherent strain (sec. 1.5.B), but not enough to preclude opening the four-membered ring. Dictyopterene C (**602**) was prepared via Cope rearrangement of the cis-diene, **601**.⁵¹⁶ The strain of the cyclopropane ring accelerated the reaction, which required heating to only 80°C. The process is effectively irreversible due to significant differences in energy between product and starting material.



- 511. Reference 80b, pp 277-278.
- 512. von E. Doering, W.; Toscano, V.G.; Beasley, G.H. Tetrahedron 1971, 27, 5299.
- 513. Hammond, G.S.; DeBoer, C.D. J. Am. Chem. Soc. 1964, 86, 899.
- 514. Brown, J.M.; Golding, B.T.; Stofko Jr., J.J. J. Chem. Soc. Chem. Commun. 1973, 319.
- 515. Evans, D.A.; Golob, A.M. J. Am. Chem. Soc. 1975, 97, 4765.
- 516. Billups, W.E.; Chow, W.Y.; Cross, J.H. J. Chem. Soc. Chem. Commun. 1974, 252.

MOLECULAR MODELING: Cope Rearrangements of *cis*-Divinylcyclopropane and *cis*-1,3-Divinylcyclobutane

The Cope rearrangement is a reversible [3,3]-sigmatropic rearrangement of a 1,5-diene. It is known that introduction of steric strain at the C_3-C_4 position of the diene, such as observed with divinylcyclopropane, leads to acceleration in the rate of rearrangement. Therefore, Cope rearrangements of *cis*-divinylcyclopropane (to *cis,cis*-1,3-cycloheptadiene) and *cis*-1,3-divinylcyclobutane (to *cis,cis*-1,3-cyclooctadiene) are faster than the corresponding Cope rearrangement of 1,5-hexadiene (to itself).

Quantum chemical calculations show that the energy barriers for rearrangement of the three and four-member ring compounds are, respectively, 77 and 40 kJ/mol lower than for rearrangement of 1,5-hexadiene. (An energy barrier is obtained by subtracting the energy of the transition state from that of the reactant.) The same calculations show that both ring opening reactions are *exothermic* (by 96 kJ/mol for divinylcyclopropane and 70 kJ/mol for divinylcyclobutane), consistent with the notion that opening a small ring leads to relief of strain. Cope rearrangement of 1,5-hexadiene leads back to 1,5-hexadiene, meaning that there is no thermodynamic driving force. Such a reaction is said to be *thermoneutral*.

Transition state structures for all three reactions are shown on screen, in addition to those for the corresponding reactants. Compare geometries of the Cope transition states for *cis*-divinylcyclopropane (top left) and *cis*-1,3-divinylcyclobutane (top center) with that of 1,5-hexadiene (bottom). In terms of carbon-carbon bond distances, which transition state is most similar to its reactant and which least similar (geometries for reactants are provided below those for transition states)? Is there a relationship between the *exothermicity* of a reaction and the degree to which the transition state resembles its reactant? Elaborate. What chemical principle are you "testing"?

Synthetic applications of the Cope rearrangement often involve interesting structural changes. The conversion of cyclopropyl ketone **603** to **604** in 58% yield is part of Ito, Iguchi and co-worker's⁵¹⁷ synthesis of clavubicyclone.



^{517.} Ito, H.; Takeguchi, S.; Kawagishi, T.; Iguchi, K. Org. Lett. 2006, 8, 4883.

The Cope rearrangement is also effective when used in conjunction with other reactions. Davies and co-workers⁵¹⁸ used a cyclopropyl-accelerated Cope rearrangement in conjunction with a rhodium-catalyzed diazoalkane cyclopropanation (sec. 13.9.C.iii). In a synthesis of the tricyclic core of vibsanin E, treatment of **605** with a dirhodium catalyst with chiral ligands led to cyclopropanation and formation of **606**, which gave the Cope rearrangement under the reaction conditions to give **607** in 69% yield and 64% ee.⁵¹⁹ The rearrangement of **606** could also be viewed as a vinylogous vinyl cyclopropane rearrangement, but the Cope mechanistic view is probably best and constitutes an effective synthesis of seven-membered ring compounds.



Majetich and Hull also showed that the presence of an enolate moiety in conjunction with the diene can facilitate the Cope rearrangement. This variation was called an **enolate accelerated Cope rearrangement**.⁵²⁰ When **608** was heated to 180°C, **610** was formed in 45% yield via bond migration from the initial Cope product, **609**. When **608** was treated with fluoride, however, enolate anion **611** was formed, and Cope rearrangement to **612** occurred at 25°C (92% yield). Hydrolysis gave **610**.



11.13.D.ii. oxy-Cope Rearrangement. Problems caused by the equilibrium inherent to the Cope rearrangement can be circumvented by the presence of an oxygen group on C3 or C4 of the diene (**598**), as mentioned above.⁵²¹ Rearrangement of **613**, for example, required heating to only 65°C (refluxing THF) to give the Cope product, which in this case is an enol (**614**) that

^{518.} Davies, H.M.L.; McAfee, M.J.; Oldenburg, C.E.M. J. Org. Chem. 1989, 54, 930.

^{519.} Davies, H M.L.; Loe, Ø.; Stafford, D.G. Org. Lett. 2005, 7, 5561.

^{520.} Majetich, G.; Hull, K. Tetrahedron Lett. 1988, 29, 2773.

^{521.} See reference 65, pp 1306-1307.

tautomerized to the ketone $(615)^{522}$ in Jung and co-worker's synthesis of coronafacic acid. When the OH unit is at C3 of the diene, the enol product is subject to keto-enol tautomerism and this shifts the equilibrium toward the final ketone product, facilitating the overall transformation.



A major factor in the rate enhancement observed for hydroxy and alkoxy dienes is the irreversibility of the reaction, assisted by formation of an enol (or enolate under basic conditions, *vide infra*), which favors the ketone form and inhibits the reverse Cope rearrangement. This alcohol variant of the Cope rearrangement is called the **oxy-Cope rearrangement**.⁵²³

Conversion of the allylic alcohol to the potassium alkoxide enhances the rate of rearrangement by a factor of up to 10¹⁰-10¹⁷, in what is called the **anionic oxy-Cope rearrangement**. This rearrangement generates an enolate anion directly, and hydrolysis gives the ketone or aldehyde. An example is taken from Castle and co-worker's synthesis of hasubanonine,⁵²⁴ where **616** was treated with *tert*-butoxide to give the alkoxide which rearranged to **617**. Subsequent hydrolysis led to **618** in 74% yield. The presence of a sulfur substituent, in addition to the alcohol unit, leads to an even greater rate acceleration.⁵²⁵ An interesting application of this reaction is **Wender's macroexpansion reaction**, in which an initial anionic oxy-Cope rearrangement of **619** generated **620**, in which the allylic groups are properly positioned for a second Cope rearrangement, giving **621**.⁵²⁶ Since this work was published, it has been argued that **620** is not an intermediate and that a [5,5]-sigmatropic rearrangement leads directly to **621**.^{526c} An antibody-catalyzed oxy-Cope reaction is known, and mechanistic studies suggest a diradical intermediate.⁵²⁷ Other bases can be used to generate the alkoxide, including phosphazene bases.⁵²⁸

^{522.} Jung, M.E.; Hudspeth, J.P. J. Am. Chem. Soc. 1980, 102, 2463.

^{523.} Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, *2005*, pp. 472-473.

^{524.} Jones, S.B.; He, L.; Castle, S L. Org. Lett. 2006; 8, 3757.

^{525.} Paquette, L.A.; Reddy, Y.R.; Vayner, G.; Houk, K.N. J. Am. Chem. Soc. 2000, 122, 10788.

^{526. (}a) Wender, P.A.; Sieburth, S.McN. *Tetrahedron Lett.* **1981**, 2471; (b) Wender, P.A.; Sieburth, S.McN.; Petraitis, J.J.; Singh, S.K. *Tetrahedron* **1981**, *37*, 3967; (c) Wender, P.A.; Ternansky, R.J.; Sieburth, S.McN. Tetrahedron Lett. 1985, 26, 4319.

^{527.} Black, K.A.; Leach, A.G.; Kalani, Y.S.; Houk, K.N. J. Am. Chem. Soc. 2004, 126, 9695.

^{528.} Mamdani, H.T.; Hartley, R.C. Tetrahedron Lett. 2000, 41, 747.



11.13.D.iii. The aza-Cope Rearrangement. It is well established that the presence of an oxygen atom adjacent to the π bond accelerates the Cope rearrangement. Overman and co-workers⁵²⁹ reported that nitrogen compounds (iminium salt fragments in the diene) undergo an **aza-Cope rearrangement**.⁵³⁰ In a synthesis of gelsemine by Overman and co-workers,⁵³¹ cyanomethylamine (622) was treated with KOH to form an imine (623) that gave the aza-Cope rearrangement to 624 (the initially formed imine isomerized to the enamine under the reaction conditions). Also under the reaction conditions, the vinyl carbonate was converted to the ketone and 625 was obtained in 81% yield. This reaction can also be viewed as an aza-Claisen rearrangement (sec. 11.12.D.iii). A recent report showed that a 3-azo-Cope rearrangement occurred using Zn²⁺-Montmorillonite clay catalysis, with microwave irradiation.⁵³²



The Cope disconnections are



532. Yadav, J.S.; Subba Reddy, B.V.; Rasheed, M.A.; Kumar, H.M.S. Synlett 2000, 487.

^{529.} Jacobsen, E.J.; Levin, J.; Overman, L.E. J. Am. Chem. Soc. 1989, 110, 4329.

^{530.} See reference 65, p 1308.

^{531.} Earley, W.G.; Jacobsen, J.E.; Madin, A.; Meier, G.P.; O'Donnell, C.J.; Oh, T.; Old, D.W.; Overman, LE.; Sharp, M.J. J. Am. Chem. Soc. 2005, 127, 18046.

11.13.E. The Claisen Rearrangement

[3,3]-Sigmatropic rearrangements are possible when heteroatoms are part of the chain linking the alkene moieties. Overman's aza-Cope rearrangement of **623** was an illustration. When that heteroatom is an oxygen as in allyl vinyl ether **626**, the [3,3]-sigmatropic rearrangement to **627** is called the **Claisen**



rearrangement.^{533,500b} Claisen rearrangements are thermal reactions⁵³⁴ usually done in solution, but a microwave-assisted reaction has been done on a solid phase.⁵³⁵ The Claisen rearrangement has been a mainstay of organic synthesis.⁵³⁶



Figure 11.23. Calculated transition state geometry for the Claisen rearrangement of allyl vinyl ether [Reprinted with permission from Yamabe; S.; Okumoto, S.; Hayashi, T. J. Org. Chem. **1996**, *61*, 6218. Copyright © 1996 American Chemical Society.]

11.13.E.i. Allyl-Vinyl Ether Rearrangements. This reaction predated the Cope rearrangement and is obviously very similar. An alkenyl carbonyl product is obtained just as in the oxy-Cope rearrangement, but the carbonyl is generated directly rather than via initial enol formation. As with the Cope rearrangement, the Claisen rearrangement proceeds via a chair-like transition state (see calculated geometry shown in Figure 11.23).⁵³⁷ The chair transition state was reported to be favored over the boat by 2.5-3.0 kcal mol⁻¹ (10.5-12.6 kJ mol⁻¹).⁵³⁸ In different work, Houk and co-workers estimated that the chair transition state for this reaction is more stable

- 535. Sampath Kumar, H.M.; Anjaneyulu, S.; Subba Reddy, B.V.; Yadav, J.S. Synlett 2000, 1129.
- 536. Martín Castro, A.M. Chem. Rev. 2004, 104, 2939.
- 537. Yamabe; S.; Okumoto, S.; Hayashi, T. J. Org. Chem. 1996, 61, 6218.
- 538. (a) Vittorelli, P.; Winkler, T.; Hansen, J.J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 1457; (b) Hansen, H.J.; Schmid, H. *Tetrahedron* **1974**, *30*, 1959.

^{533. (}a) Claisen, L. Berichte 1912, 45, 3157; (b) Claisen, L.; Tietze, E. Ibid. 1925, 58, 275; (c) Idem Ibid. 1926, 59, 2344; (d) Tarbell, D.S. Org. React. 1944, 2, 1; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-18; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 156-159.

^{534.} See reference 65, pp 1302-1303.

than the boat transition state by about 6.6 kcal mol⁻¹ (27.6 kJ mol⁻¹).⁵³⁹ Ziegler reviewed the synthetic applications of the Claisen rearrangement, and the stereoselectivity that characterizes this reaction is apparent in those applications.⁵⁴⁰ A generic Claisen rearrangement is illustrated by allyl vinyl ether **628**, which rearranges to **630** via chair transition state **629**. The two methyl groups are equatorial in the transition state, a result of the (*E*,*E*)-geometry in **628**.^{540,538}



The (E,Z)- and (Z,Z)-derivatives will rearrange more slowly since one or both of the methyl groups will be axial in the transition state (**629**). When a substituent is present at C4 (see **626**), the substituent prefers the equatorial position in the transition state. The selectivity is about 99% when an alkyl group is present rather than a hydrogen (greater selectivity is observed when the substituents are -OR or -NR₂).^{540,541} The energy requirements and stereochemical arguments



are virtually identical with those discussed for the Cope rearrangement. A synthetic example is taken from a synthesis of garsubellin A,⁵⁴² in which Shibasaki and coworkers heated allyl vinyl ether **631** to 200°C in the presence of

sodium acetate and obtained **632** in 96% yield. The allyl vinyl ether is a precursor to molecules containing both an aldehyde (or ketone) and an alkene.

The Claisen rearrangement is not restricted to aliphatic derivatives. Rearrangement occurs with aryl allyl ethers such as **633**, which gave **634** in 80% yield, in Theodorakis and co-worker's synthesis of the cyclic core of *Garcinia* natural products.⁵⁴³ These rearrangements can be sluggish, and a Lewis acid catalyst such as TiCl₄ is sometimes required.⁵⁴⁴



^{539.} Vance, R.L.; Rondan, N.G.; Houk, K.N.; Jensen, F.; Borden, W.T.; Komornicki, A.; Wimmer, E. J. Am. Chem. Soc. 1988, 110, 2314.

^{540.} Ziegler, F.E. Acc. Chem. Res. 1977, 10, 227.

^{541.} Faulkner, D.J.; Petersen, M.R. Tetrahedron Lett. 1969, 3243.

^{542.} Kuramochi, A.; Usuda, H.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. J. Am. Chem. Soc. 2005, 127, 14200.

^{543.} Tisdale, E.J.; Chowdhury, C.; Vong, B.G.; Li, H.; Theodorakis, E.A. Org. Lett. 2002, 4, 909.

^{544.} For an example, see Saidi, M.R. Heterocycles 1982, 19, 1473.

A catalyst is not always necessary for the Claisen rearrangement to occur.⁵⁴⁵

Lewis acids catalyze the Claisen rearrangement, often with improved stereoselectivity. Acyclic allyl vinyl ethers give a Claisen rearrangement upon treatment with a catalytic amount of Pd(II).⁵⁴⁶ A Ho(fod) catalyst has been used as well.⁵⁴⁷ An example of this type of reaction is the conversion of **635** to a 22:71 mixture of **636** and **637** in 99% yield.⁵⁴⁸



MOLECULAR MODELING: Stereochemistry of Claisen Rearrangements

Two enantiomeric products are typically formed in a Claisen rearrangement. In other words, the reaction gives a racemic product. When there is stereogenic center close to the reactive atoms, however, the substituent on that center acts as a "controller group" to generate a product enantioselectivity. For example, while Claisen rearrangement of (S)-4-(6-methyl-E-2-heptenyl) vinyl ether may lead to two different enantiomeric products, in fact, a single product is formed in >96% abundance.



Shown on screen are the two chair transition states that lead to the two different enantiomeric products. Choose the one that you think should be the lower in energy, and justify your selection. Hint. Consider the conformational analysis of six-membered rings in **Chapter 1**. Which of the two products shown corresponds to the product that results from the transition state you have chosen?

11.13.E.ii. Variants of the Claisen Rearrangement. Many methods are used to prepare the allyl vinyl ether precursors required for the Claisen rearrangement. Many of these preparations are rather specialized variations, usually named after the scientist(s) who developed them. One method used for the preparation of allyl vinyl ethers (640) is the acid catalyzed reaction of vinyl ethers such as 638 and allyl alcohols such as 639. Vinyl ether 640 is formed *in situ* but usually not isolated since a Claisen rearrangement occurs under the reaction conditions to

^{545.} Subramanian, R.S.; Balasubramanian, K.K. Tetrahedron Lett. 1988, 29, 6797.

^{546. (}a) van der Baan, J.L.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, 27, 6267; (b) Sugiura, M.; Nakai, T. *Chem. Lett.* **1995**, 697; (c) Hiersemann, M. *Synlett* **1999**, 1823.

^{547.} Trost, B.M.; Schroeder, G.M. J. Am. Chem. Soc. 2000, 122, 3785.

^{548.} Hiersemann, M.; Abraham, L. Org. Lett. 2001, 3, 49.

give **641**. This transformation has been termed the **Marbet-Saucy variant**⁵⁴⁹ of the Claisen rearrangement (**Marbet-Saucy or Saucy-Marbet reaction**). A synthetic example is the treatment of **642** with 3-methoxyisoprene to generate **643** as a reactive intermediate. Subsequent Claisen rearrangement gave **644** in Faulkner and co-worker's synthesis of squalene.⁵⁵⁰ Hsung and co-workers applied this reaction to the synthesis of highly substituted chiral homoallenyl alcohols using chiral ynamides.⁵⁵¹



A similar variant of the Claisen rearrangement reacts allyl alcohols such as **645** with β -bromoselenides (**646**) to give **647**. Oxidation to the transient selenoxide (**648**) and *in situ* syn-elimination (sec. 2.9.C.vi) gave **649**. This ether possessed the proper functionality for Claisen rearrangement to the final product, ester **650**.⁵⁵² Petrzilka used a variation of this method for the synthesis of phoracantholide J.⁵⁵³



Carrol prepared the allyl ester of β -keto acids, which exist largely as the enol, and give a Claisen rearrangement to a β -keto acid.⁵⁵⁴ This reaction is usually called the **Carroll variant**,

^{549.} Marbet Saucy, G. Helv. Chim. Acta 1967, 50, 2091, 2095.

^{550.} Faulkner, D.J.; Petersen, M.R. J. Am. Chem. Soc. 1973, 95, 553.

^{551.} Frederick, M.P. Hsung, R.P.; Lambeth, R.H.; Mulder, J.A.; Tracey, M.R. Org. Lett. 2003, 5, 2663.

^{552.} Petrzilka, M. Helv. Chim. Acta 1978, 61, 2286.

^{553.} Petrzilka, M. Helv. Chim. Acta 1978, 61, 3075.

^{554.} Tanabe, M.; Hayashi, K. J. Am. Chem. Soc. 1980, 102, 862.

the **Carroll-Claisen rearrangement** or the **Carroll reaction**,⁵⁵⁵ although it has also been called the **Kimel-Cope rearrangement**.⁵⁵⁶ Decarboxylation is facile at this reaction temperature. Heating **651** on neutral alumina led to Carroll reaction that was accompanied by loss of CO₂ to give a 72% yield of **652**, in Cossy, Meyer and co-worker's synthesis of zincophorin methyl ester,⁵⁵⁷ Wilson introduced a variation of the Carrol reaction with mild conditions for the rearrangement.⁵⁵⁸ Dianions of allylic acetoacetates rearrange at room temperature or in refluxing THF. When **653** was heated to 170°C for 2 h (neat), 50% of a mixture (67:33) of **654** and **655** was obtained. When **653** was treated with two equivalents of LDA (sec. 9.2.B and 9.4.B.vii), however, the enolate dianion rearranged in refluxing THF and subsequent decarboxylation in refluxing carbon tetrachloride led to an 84% yield of **654** with no **655**.⁵⁵⁸



Another variation of the Claisen rearrangement involves ketene acetals, which are generated by reaction of allylic alcohols with ortho esters $[R^1CH_2C(OEt)_3]$ under acidic conditions. The resulting product (656) eliminates ethanol to give 657, and this product undergoes a Claisen rearrangement to give ester 658. This sequence is known as the Johnson-ester variant⁵⁵⁹

⁽a) Carroll, M.F. J. Chem. Soc. 1940, 704, 1266; (b) Idem Ibid. 1941, 507; (c) Reference 80b, p 300-302;
(d) Ziegler, F.E. Chem. Rev. 1988, 88, 1423; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-16; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 134-135.

^{556.} Kimel, W.; Cope, A.C. J. Am. Chem. Soc. 1943, 65, 1992.

^{557. (}a) Defosseux, M.; Blanchard, N.; Meyer, C.; Cossy, J. Org. Lett. 2003, 5, 4037; (b) Idem J. Org. Chem. 2004, 69, 4626.

^{558.} Wilson, S.R.; Price, M.F. J. Org. Chem. 1984, 49, 722.

^{559. (}a) Johnson, W.S.; Werthemann, L.; Bartlett, W.R.; Brocksom, T.J.; Li, T.T.; Faulkner, D.J.; Petersen, M.R. J. Am. Chem. Soc. 1970, 92, 741; (b) Johnson, W.S.; Gravestock, M.B.; Parry, R.J.; Myers, R.F.; Bryson, T.A.; Miles, H. Ibid. 1971, 93, 4330; (c) Reference 80b, p 302-308; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 350-351.

of the Claisen rearrangement, or the **ortho ester Claisen rearrangement.**⁵⁶⁰ An example is taken from a synthesis of (–)-cucumin H by Srikrishna and Dethe, in which allylic alcohol **659** was heated with triethyl orthoacetate in propionic acid to give an 80% yield of the Claisen rearrangement product **661** via **660**.⁵⁶¹



A related variation was reported by Eschenmoser, who showed that heating an allylic alcohol with *N*,*N*-dimethylacetamide dimethyl acetal (**662**) gave **663**. This transient intermediate eliminated methanol to give **664**, and subsequent Claisen rearrangement generated amide **665** in a sequence that is known as the **Eschenmoser variant** or the **Eschenmoser-Claisen rearrangement**.⁵⁶² Corey and co-worker's synthesis of thromboxane B₂ utilized this methodology.⁵⁶³ Another synthetic example is the conversion of **666** to **667** in good yield, as part of Kobayashi and co-worker's synthesis of tuberonic acid.⁵⁶⁴



^{560.} For a discussion of acyclic stereoselection in this reaction, see Daub, G.W.; Edwards, J.P.; Okada, C.R.; Allen, J.W.; Maxey, C.T.; Wells, M.S.; Goldstein, A.S.; Dibley, M.J.; Wang, C.J.; Ostercamp, D.P.; Chung, S.; Cunningham, P.S.; Berliner, M.A. J. Org. Chem. 1997, 62, 1976.

- 563. Corey, E.J.; Shibasaki, M.; Knolle, J. Tetrahedron Lett. 1977, 1625.
- 564. Nonaka, H.; Wang, Y.-G.; Kobayashi, Y. Tetrahedron Lett. 2007, 48, 1745..

^{561.} Srikrishna, A.; Dethe, D.H. Org. Lett. 2003, 5, 2295.

^{562. (}a) Felix, D.; Gschwend-Steen, K.; Wick, A.E.; Eschenmoser, A. Helv. Chim. Acta 1969, 52, 1030; (b) Reference 80b, pp. 309-311.

Esters can be converted to the corresponding enolate via treatment with base and can rearrange, as observed by Arnold and Hoffman.⁵⁶⁵ When the enolate was trapped as the *O*-trialkylsilyl ether, a 1,5-diene was generated that gave a Claisen rearrangement under milder conditions. The solvent has a great influence on the selectivity of the reaction, and THF is commonly used.⁵⁶⁶ The enolate Claisen rearrangement occurs at ambient temperatures, whereas most Claisen rearrangements require temperatures of 120-200°C.⁵⁶⁷ The enolate accelerated Claisen rearrangement is obviously similar to the enolate accelerated Cope rearrangement described by Majetich in sec. 11.12.C.⁵²⁰ If hexamethylphosphoramide (HMPA) is added, the lithium ion (Li⁺) is solvated. Lithium coordination with oxygen is poor and the syn-isomer predominates. If THF is used, $O \Leftrightarrow$ Li coordination is strong and the anti-isomer is the major product.

In section 9.4.B,C, an ester such as **668** reacted with LDA under kinetic control conditions to form enolate anion **669**, which then reacted with chlorotrimethylsilane to give silyl enol ether **670**. Compounds such as **670** were prepared by Ireland and Mueller, who found that subsequent Claisen rearrangement followed by hydrolysis of the initially formed silyl ester gave acid **671**, in what has come to be known as the **Ireland variant** or the **Ireland-Claisen rearrangement**.⁵⁶⁸ There are several stereoselective variations of this reaction.⁵⁶⁹ An example of the reaction is taken from a synthesis of galbonolide B by Parsons and co-workers,⁵⁷⁰ in which formation of the silyl enol ether of ester **672** under the conditions shown led to a 75% yield of the corresponding acid **673**.



565. Arnold, R.T.; Hoffmann, C. Synth. Commun. 1972, 2, 27.

- 566. Ireland, R.E.; Mueller, R.H.; Willard, A.K. J. Am. Chem. Soc. 1976, 98, 2868.
- 567. Reference 80b, p 312.
- 568. (a) Ireland, R.E.; Mueller, R.H. J. Am. Chem. Soc. 1972, 94, 5897; (b) Pereira, S.; Srebnik, M. Aldrichimica Acta 1993, 26, 17; (c) Reference 80b, p 311-319; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 340-341.
- 569. Chai, Y.; Hong, S-p.; Kubdsaym H.A.; McFarland, C.; McIntosh, M.C. Tetrahedron 2002, 58, 2905.
- 570. Parsons, P.J.; Pennicott, L.; Eshelby, J.; Goessman, M.; Highton, A.; Hitchcock, P.J. Org. Chem. 2007, 72, 9387.

MOLECULAR MODELING: Ireland-Claisen Rearrangement

The Ireland-Claisen rearrangement involves formation of an enolate anion of an allylic ester. Signatropic rearrangement leads to a carboxylic acid product. The enolate anion of 672 is trapped by reaction with trimethylsilyl chloride to give a mixture of *E* and *Z* stereoisomers of the intermediate **A**. Each may undergo a Claisen rearrangement (presumably via a chair transition state), leading first to the intermediate **B** and finally to 673. The stereochemistry of the product is determined in the reaction between intermediates **A** and **B**.



Quantum chemical calculations show that the transition state arising from the Z stereoisomer of A is 10 kJ/mol lower in energy than the transition state arising from the E stereoisomer. Examine the two transition states and, based on conclusions reached in previous molecular modeling problems, provide a reason for the preference.

Rate enhancement is possible, especially the enolate Claisen rearrangement. Denmark et al.⁵⁷¹ showed that other carbanionic centers accelerate the Claisen rearrangement. Generation of the anion of sulfone **674** (sec. 8.6.A) with various bases led to acceleration of the reaction relative to the thermal reaction of **674** and also influenced the syn/anti ratio (**675/676**), generally favoring **675**. In general, a donor group at the allyl position accelerates the rate and the presence of an amino stabilizing group increases the rate even more.





Aqueous solvents can accelerate the Claisen rearrangement in many cases, as observed in the Diels-Alder reaction (sec. 11.6.B). McMurry et al. showed that heating **677** to 360°C gave only a 20% yield of **678** in a synthesis of aphidicolin.⁵⁷² The difficulty lay in the sensitivity of the product to

^{571. (}a) Denmark, S.E.; Harmata, M.A.; White, K.S. J. Am. Chem. Soc. 1989, 111, 8878; (b) Denmark, S.E.; Harmata, M.A. Ibid. 1982, 104, 4972.

^{572.} McMurry, J.E.; Andrus, A.; Ksander, G.M.; Musser, J.H.; Johnson, M.A. Tetrahedron 1981, 37 (Suppl 1), 319.

the reaction conditions and the steric hindrance to formation of the correct chair transition state. When Grieco and co-workers heated the water soluble diol **679** to 80°C an 85% yield of **680** was obtained,⁵⁷³ which dramatically demonstrated the rate enhancement possible in aqueous solvents.



As with Diels-Alder reactions, solubility of the Claisen precursor in the aqueous medium is required.



Many transition metal compounds catalyze the Claisen rearrangement⁵⁴⁴ (see the reaction of **637** with copper triflate cited above). Aluminum reagents such as **681** or **682** can also catalyze the Claisen rearrangement

with opposite stereochemistry, as reported by Yamamoto and co-workers.574



Palladium chloride (PdCl₂) is known to catalyze the rearrangement of allyl ethers in a reaction that looks very much like a Claisen transition state. Treatment of **683** with PdCl₂, for example, initially generated the π -palladium complex (**684**) that was attacked by the carbonyl oxygen to give **685**, and ring opening gave the rearrangement product **686**.^{575,576} It is important to note, however, that this reaction proceeds in a step-wise manner via a π -allyl palladium intermediate and not via a concerted [3,3]-sigmatropic rearrangement (sec. 12.6 for a discussion of palladium-catalyzed reactions). Therefore, one must exercise care in categorizing reaction types. It is

included here only because of the similarity in products obtained by this process and is not meant to imply that it proceeds by an identical mechanism to the Claisen rearrangement. Grieco



^{573.} Grieco, P.A.; Brandes, E.B.; McCann, S.; Clark, J.D. J. Org. Chem. 1989, 54, 5849.

^{574.} Nonoshita, K.; Banno, H.; Maruoka, K.; Yamamoto, H. J. Am. Chem. Soc. 1990, 112, 316.

^{575.} Henry, P.M. J. Am. Chem. Soc. 1972, 94, 5200.

^{576.} Kitching, W.; Rappoport, Z.; Winstein, S.; Young, W.G. J. Am. Chem. Soc. 1966, 88, 2054.

and co-workers used a similar palladium catalyzed Claisen rearrangement to convert **687** to **688** (93% yield) in a synthesis of 15-epi-12-methyl prostaglandin $F_{2\alpha}$.⁵⁷⁷

11.12.E.iii. thio-Claisen and aza-Claisen Rearrangements. Heteroatoms other than oxygen can be used. The two most common are sulfur and nitrogen (giving thio-Claisen and aza-Claisen rearrangements, respectively). Heating allyl vinyl sulfides (689) leads to a



 $H_{3}O^{+}$ $H_{3}O^{+}$ H_{691} H_{691} H_{691} H_{691} [3,3]-rearrangement that gives thioaldehyde 690, and subsequent hydrolysis generates an aldehyde $691.^{578}$ This variant is known as the thio-Claisen rearrangement. 579

The thio-Claisen rearrangement was the basis of an **umpolung** reagent discussed in Section 8.6.B.vi. Treatment of **689** with *sec*-butyllithium gave the α -lithio sulfide (**692**), and condensation with benzyl bromide gave the alkylated sulfide, **693**. Heating led to a thio-Claisen rearrangement and hydrolysis of the resulting product gave aldehyde **694** in 62% overall yield.⁵⁸⁰ This sequence was correlated with umpolung equivalent **695**.⁵⁸⁰



Iminium salts have been used in **aza-Claisen rearrangement** reactions (also see the aza-Cope rearrangement in sec. 11.12.C.iii).^{530,581} In the generic reaction, heating *N*-allylic enamines led to an imine that could be hydrolyzed to an aldehyde,⁵⁸² or converted to another nitrogencontaining moiety. Lewis acids such as titanium tetrachloride (TiCl₄) catalyze the aza-Claisen rearrangement. When aldehyde **696** reacted with 3-(*N*-phenyl)-1-butene (**697**) in the presence of TiCl₄, the initially formed enamine (**698**) rearranged to **699** and was hydrolyzed to aldehyde **700** in 61% overall yield.⁵⁸³



^{577.} Grieco, P.A.; Takigawa, T.; Bongers, S.L.; Tanaka, H. J. Am. Chem. Soc. 1980, 102, 7587.

- 578. Oshima, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. J. Am. Chem. Soc. 1973, 95, 2693.
- 579. Majumdar, K.C.; Ghosh, S.; Ghosh, M. Tetrahedron 2003, 59, 7251.
- 580. Takano, S.; Hirama, T.; Araki, T.; Ogasawara, K. J. Am. Chem. Soc. 1976, 98, 7084.
- 581. Makisumi, Y. Tetrahedron Lett. 1966, 6413.
- 582. Hill, R.K.; Gilman, N.W. Tetrahedron Lett. 1967, 1421.
- 583. Hill, R.K.; Khatri, H.N. Tetrahedron Lett. 1978, 4337.

Stille and Cook developed an attractive route to aza-Claisen precursors. Allylamine reacted with 2-methylpropanal (isobutyraldehyde), for example, to give allyl imine **701**.⁵⁸⁴ When **701** reacted with 2-methylpropanoyl chloride, *N*-acyl derivative **702** was produced (94% overall yield from allylamine) and reduction with LiAlH₄ give a 98% yield of tertiary amine **703**. Stille found that conversion of the amine to the ammonium salt by treatment with HCl led to clean conversion to **704** in 82% yield via a [3,3]-sigmatropic rearrangement (an aza-Claisen rearrangement). Reduction of the iminium salt led to an 81% yield of **705** from **704**. Stille and co-workers also found that Lewis acids as well as HCl react with the allyl enamine precursor to facilitate the aza-Claisen rearrangement.⁵⁸⁵



Other types of iminium salts can be used this reaction. β -Carboline **706** was reduced and converted to iminium salt **707** by treatment with formaldehyde (secs. 4.4.B, 4.10.D). The aza-Claisen rearrangement (sometimes called the **2-azonia rearrangement** in this system) was used by Winterfeldt and co-workers⁵⁸⁶ to generate 15 β -methoxyyohimban-17-ol).



The Claisen rearrangement disconnections are



^{584. (}a) Cook, G.R.; Stille, J.R. J. Org. Chem. 1991, 56, 5578; (b) Cook, G.R.; Barta, N.S.; Stille, J.R. Ibid. 1992, 57, 461.

^{585.} Barta, N.S.; Cook, G.R.; Landis, M.S.; Stille, J.R. J. Org. Chem. 1992, 57, 7188.

^{586.} Ahmad, V.U.; Feuerherd, K.H.; Winterfeldt, E. Chem. Ber. 1977, 110, 3624.

11.14. THE ENE REACTION

The Diels-Alder reaction is a thermal cycloaddition involving 1,3-dienes and alkenes, and [3+2]-cyclo-addition reactions involve a π bond and a 1,3-dipole. The Cope, oxy-Cope and Claisen rearrangements are thermal, intramolecular reactions of 1,5-dienes. A [2+2]-cycloaddition usually involves reaction between two alkenes, or certainly two π bonds. A reaction that is different from any seen so far occurs with certain alkenes and allylic systems. In its fundamental form, it is "the indirect substituting of a compound with a double bond (**enophile**) to an alkene that has an allylic hydrogen (the **ene**)"⁵⁸⁷ to give a new, substituted alkene. This transformation is called the **ene reaction**.⁵⁸⁸ Although several related examples of this reaction were reported early in the 20th century,⁵⁸⁷ it was not until the work of Alder and coworkers in 1943⁵⁸⁹ that the ene reaction was recognized as a synthetically useful tool. Because of this work, this transformation is often referred to as the **Alder ene reaction**. Oppolzer often used magnesium-ene cyclizations in syntheses.⁵⁹⁰ Oppolzer and co-workers also developed a Pd-catalyzed Zn-ene cyclization using allyl acetate precursors.⁵⁹¹

11.14.A. Enes and Enophiles



The ene reaction involves an alkene fragment (the ene) that removes a hydrogen from an allylic fragment with formation of a new carbon bond, as in **708**.^{592,264} As with the other reactions in this chapter, reactivity and stereochemistry in the ene reaction can be explained

by frontier orbital theory. The reaction proceeds via interaction of the HOMO of the alkene (ene) and the LUMO of the allylic partner (enophile),⁵⁹³ illustrated by the reaction of propene and ethene in Figure 11.24, with the transition structure calculated by Houk and Loncharich.⁵⁹⁴ The intermolecular reaction usually requires very high temperatures (typically 250-600°C). 2-Methylpropene reacts with acetylene to give a 40% yield of 2-methyl-1,4-pentadiene, for example, but the reaction requires a large excess of isobutylene at 170 atmospheres.⁵⁹⁵ The fact

^{587.} Hoffmann, H.M.R. Angew. Chem. Int. Ed. 1969, 8, 556.

^{588. (}a) See reference 65, p 236; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-28; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 226-227.

^{589.} Alder, K.; Pascher, F.; Schmitz, A. Berichte 1943, 76, 27.

⁽a) Oppolzer, W. Angew. Chem. Int. Ed. 1989, 28, 38; (b) Oppolzer, W. Pure Appl. Chem. 1990, 62, 1941;
(c) Oppolzer, W. in Comprehensive Organic Synthesis, Trost, B.M., Ed., Pergamon Press, New York, 1991, Vol. 5, pp 29-61.

^{591. (}a) Oppolzer, W.; Schröder, F. Tetrahedron Lett. 1994, 35, 7939; (b) See Yasui, K.; Goto, Y.; Yajima, T.; Taniseki, Y.; Fugami, K.; Tanaka, A.; Tamaru, T. Tetrahedron Lett. 1993, 34, 7619.

^{592.} Taber, D.F. Reactivity and Structure Concepts in Organic Chemistry, Vol. 18, Springer-Verlag, Berlin, 1984.

^{593.} Oppolzer, W.; Snieckus, V. Angew. Chem. Int. Ed. 1978, 17, 476.

^{594.} Loncharich, R.J.; Houk, K.N. J. Am. Chem. Soc. 1987, 109, 6947.

^{595.} Cywinski, N.F. J. Org. Chem. 1965, 30, 361.



that the reaction is concerted (rather than involving a cationic intermediate) can be illustrated by the ene reaction of β -pinene (**709**) and maleic anhydride to give **710**, without skeletal rearrangement of the pinene ring.⁵⁹⁶ In general, allylic alkenes

react faster than allylic alkynes in the ene reaction.⁵⁸⁷ This point is illustrated by the vigorous conditions of the previously cited reaction of acetylene. If the alkene contains a strained double bond, the ene reaction is accelerated (lower reaction temperatures). Caryophyllene

(711) contains a strained trans-double bond and gave an ene reaction with maleic anhydride under very mild conditions (refluxing benzene) to give 712, but the yield was only 19%.⁵⁹⁷



Figure 11.24. Calculated Transition State For the Alder Ene Reaction of Propene And Ethylene. [Reprinted with permission from Loncharich, R.J.; Houk, K.N. J. Am. Chem. Soc. **1987**, 109, 6947. Copyright © 1987 American Chemical Society.]

MOLECULAR MODELING: Transition State for an Ene Reaction

Transition states for chemical reactions cannot be observed experimentally, simply because they are not energy minima and do not form collections on which measurements may be made. However, the structures, energies and "properties" of transition states may be calculated. Propene and maleic anhydride undergo an ene reaction to yield allylsuccinic anhydride.



The transition state for this reaction is displayed on screen. Measure bond distances for the C–C bonds that are broken and formed and compare these to the corresponding distances in the reactants. Build propene. *Click* on > and then select *Continue* to get a model-building palette. Repeat the process for

^{596.} Arnold, R.T.; Showell, J.S. J. Am. Chem. Soc. 1957, 79, 419.

^{597. (}a) Nickon, A. J. Am. Chem. Soc. 1955, 77, 1190; (b) Ruzicka, L.; Plattner, P.A.; Balla, G. Helv. Chim. Acta 1941, 24, 1219; (c) Ruzicka, L.; Zimmerman, W. Ibid. 1935, 18, 219; (d) Rydon, H.N.J. Chem. Soc. 1939, 537.

MOLECULAR MODELING: Transition State for an Ene Reaction, con't.

maleic anhydride. Describe changes to C–C bond distances in going from reactants to transition state. Are the changes to the C–O single and double bonds as large as those to the C–C bonds? Is the migrating hydrogen bound more tightly to propene or to the product (or is it roughly midway in between)?

The "infrared spectrum" of a transition state cannot be observed, but it can be calculated. Each line in the spectrum corresponds to a vibration that a molecule undergoes. The frequency of the line is proportional to the *square root* of the so-called force constant, that is, the difficulty of moving ("up") from an energy well. Motions that are "easy" (for example, changes in torsional angles) give rise to low frequencies, whereas motions that are "difficult" (for example, CH bond stretches) give rise to high frequencies. One vibration in the infrared spectrum of a transition state corresponds to a "downhill" motion, that is, the force constant is negative. Taking the square root gives rise to an imaginary frequency. *Click* on this frequency in the spectrum (designated as "negative" 1500 cm⁻¹) to see the motion. Is it almost entirely associated with the migrating hydrogen or do other atoms move as well?

Carbonyl compounds are enophiles in the ene reaction, particularly when the enophilic carbonyl is conjugated to another carbonyl moiety. Diethyl mesoxalate (**713**), for example, reacted with 1-pentene to give **714**.⁵⁹⁸

+ CO_2Et TI3 CO_2Et CO_2Et OH CO_2Et OH CO_2Et

Intramolecular ene reactions have been studied in great detail.^{599,405} The most common ene precursors are 1,6- and 1,7-dienes, with 1,6-dienes the more reactive and more useful. The



 $\begin{bmatrix} H \\ H \\ T17 \end{bmatrix} \xrightarrow{H} H$ product of the ene reaction of a 1,6-diene is a five-membered ring derivative. Cyclization of 1,6-octadiene (715, a cis-trans mixture) at 457°C⁶⁰⁰ gave exclusively cis-isomer 717 in 35% yield,

via a transition state that is believed to resemble **716**. Note that internal ene reactions typically give a mixture of diastereomers.⁶⁰¹

Oppolzer et al. described the stereochemistry for cis- and trans-enophiles in the ene reaction. When amide **718** containing a cis- alkene unit and amide **720** containing a trans-alkene unit reacted via an ene reaction, the same product (**719**) was formed.⁶⁰² The temperature used for the reaction had a large influence on product distribution and stereochemistry. Cyclization of

^{598.} Achmatowicz, O.; Achmatowicz, Jr., O. Roczniki Chim. 1962, 36, 1791 [Chem. Abstr. 59: 8610b 1963].

^{599.} Reference 592, p 61-94.

^{600.} Huntsman, W.D.; Solomon, V.C.; Eros, D. J. Am. Chem. Soc. 1958, 80, 5455.

^{601.} Pines, H.; Hoffman, N.E.; Ipatieff, V.N. J. Am. Chem. Soc. 1954, 76, 4412.

^{602.} Oppolzer, W.; Pfenninger, E.; Keller, K. Helv. Chim. Acta 1973, 56, 1807.

721 at 450°C, for example, gave a mixture of **722**, **723** and **724** (9:25:41). Ene reaction of **721** at 290°C gave the same products, but in a ratio of 2:7:40.⁶⁰³ Good selectivity is possible in the ene reaction, as in the conversion of **725** to **726** in 60% yield at 250°C, in Stork's explorations toward the synthesis of prostaglandins.⁶⁰⁴ In this case, the silyl group on the secondary hydroxyl was selectively removed by treatment with dilute HCl in THF (sec. 7.3.A.i). This selectivity may be due to increased steric hindrance at that position or to a rate-determining oxygen protonation step, or both.⁶⁰⁴ Oppolzer and Bättig used an ene reaction to convert **727** to **729** via an endo-transition state (see **728**) in a synthesis of modhephene, with good selectivity.⁶⁰⁵ The conformational constraints imposed by the molecular structure of the ene led to high selectivity in the rearrangement products. Conjugated alkynes are also enophiles.⁶⁰⁶



^{603.} Schulte-Elte, K.H.; Gadola, M.; Ohloff, G. Helv. Chim. Acta 1971, 54, 1813.

^{604.} Stork, G.; Kraus, G. J. Am. Chem. Soc. 1976, 98, 6747.

^{605.} Oppolzer, W.; Bättig, K. Helv. Chim. Acta 1981, 64, 1575.

^{606.} Takahashi, K.; Mikami, K.; Nakai, T. Tetrahedron Lett. 1988, 29, 5277.

MOLECULAR MODELING: Transition-State Structures Anticipate Kinetic Product Distributions

Some ene reactions may give rise to two or more isomeric products. If the reaction is under kinetic control, the preferred product (and more generally, the distribution of products) may be anticipated by comparing the energies of transition states leading to the different products. A good example is provided by the intramolecular ene reaction of diene \mathbf{A} , which is known to give primarily \mathbf{B} rather than \mathbf{C} .



The two pertinent transition state models obtained from quantum chemical calculations are provided on screen. The structure on the left is 8 kJ/mol lower in energy that that on the right. Draw the product that results from this transition state and confirm that it leads to the dominant product. Why do you think that the transition state on the left more stable?

Lewis acids are effective catalysts for the ene reaction in many ene-ene or ene-yne reactions, although they are most effective with carbonyl ene reactions (see below). Buchwald and co-workers,⁶⁰⁷ for example, reported a titanocene-catalyzed intramolecular ene reaction in which ene-yne **730** was treated with Cp₂Ti(CO)₂ in hot toluene to give a 97% yield of ene product **731**.



11.14.B. Ene Reactions of 1,7-Dienes

Ene reactions of 1,7-dienes are less common. Both six-membered ring products (such as **732** via path *a*) and eight-membered ring products (such as **733** via path *b*) are possible.⁵⁸⁷ The first ene reaction with a 1,7-diene was probably reported by Hunstman et al.⁶⁰⁸ Six-membered rings are usually preferred to eight- membered rings, but ene reactions of 1,7-dienes require higher reaction temperatures. Heating 8-methyl-1,7-nonadiene (**734**, R = H) to 440°C, for example, gave no reaction although a good yield of **735** was obtained at 490°C.⁶⁰⁴ The

^{607.} Sturla, S.J.; Kablaoui, N.M.; Buchwald, S.L. J. Am. Chem. Soc. 1999, 121, 1976.

^{608.} Hunstman, W.D.; Lang, P.C.; Madison, N.L.; Uhrick, D.A. J. Org. Chem. 1962, 27, 1983.

presence of a carbomethoxy group led to a more facile ene reaction in which **734** (R = CO_2Me) was converted to **735** in about 25% yield, but still required a temperature of 400°C.⁶⁰⁸



The presence of an electron-withdrawing group increases the rate of the ene reaction by lowering the LUMO energy. Lewis acids greatly enhance the rate of ene reactions involving 1,7-dienes.⁶⁰⁹ When **736** was treated with zinc bromide (ZnBr₂) the ene reaction occurred at room temperature to give an 88% yield of desmethyl **737**/**738** (>99:1 favoring **737**).^{609a,610}



MOLECULAR MODELING: Nature of the Migrating Hydrogen in an Ene Reaction

Observed variation in rate among closely-related reactions can sometimes provide insight into the nature of the reaction. For example, the intramolecular ene reaction of **734** with R=H requires heating to 490°C, whereas the corresponding reaction with R=CO₂Me readily occurs at 400°C. This observation suggests that the migrating hydrogen bears "negative charge", that is, it is stabilized by an electron-accepting group at the "receiving end".

Examine the electrostatic potential map for transition state for reaction with R=H (left). Recall that this map colors an electron density surface which gives to overall molecular size and shape with the value of the electrostatic potential (the energy of a point positive charge with the nuclei and electrons of a molecule). By convention, electron-rich regions (negative) on are "red", electron-deficient regions (positive) are "blue" and neutral regions are "green". The maps are displayed as transparent models to allow you to see the underlying structure. Once you are oriented with regard to the position of the migrating hydrogen, switch to solid models by *clicking* on one of the maps and

^{609. (}a) Tietze, L.F.; Beifuss, U. Angew. Chem. Int. Ed. 1985, 24, 1042; (b) Idem Liebigs Ann. Chem. 1988, 321; (c) Nakatani, Y.; Kawashima, K. Synthesis 1978, 147; (d) Sakane, S.; Maruoka, K.; Yamamoto, H. Tetrahedron 1986, 42, 2203.

^{610.} Tietze, L.F.; Beifuss, U.; Ruther, M. J. Org. Chem. 1989, 54, 3120.

MOLECULAR MODELING: Nature of the Migrating Hydrogen in an Ene Reaction, con't.

selecting *Solid* from the **Style** menu at the bottom of the screen. Is the migrating hydrogen negatively charged, positively charged or neutral? What does this suggest about the ability of an electron-withdrawing group such as acetate to stabilize the transition state? Next, examine the electrostatic potential map for transition state for reaction with $R=CO_2Me$ (right). Is either the direction and/or magnitude of the charge on the migrating hydrogen significantly different than that for the reaction with R=H? Are your results consistent with the observed rate change? Elaborate.

11.14.C. Carbonyl and Imino Ene Reactions

When a carbonyl moiety is the ene component of a 1,6- or 1,7-diene system, the ene reaction is more favorable. Heating **739** to 110°C, for example, led to a 94% yield of **740** in White and Somers' synthesis of 2-desoxystemodinone.⁶¹¹ In **739**, the 1,6-diene is the π -bond of the aldehyde carbonyl and the π bond of the cyclohexene unit, which is more easily seen in the conformational drawing. The reaction occurred in refluxing toluene in good yield, and with excellent stereoselectivity due to the rigid nature of the tricyclic system.



MOLECULAR MODELING: Models vs. 2D Sketches

The design of new total syntheses requires the ability to reliably "guess" the products of the individual steps in the overall sequence of reactions. This is why we study organic reactions, and place so much emphasis on three-dimensional structure (stereochemistry). It seems odd then that chemists use 2D drawings and not 3D models to display structures. An example of the limitations of 2D drawings is provided by the ene reaction of **739**, where the stereochemistry of the product depends on the "reactive" conformation of the aldehyde. Even though there are only 9 conformers (threefold rotation around the hydroxyl group and threefold rotation of the aldehyde), merely looking at the drawing does not easily reveal the stereochemistry of the product.

Obtain energies for different conformers of **739** to identify the one with the lowest energy. To rotate around a single bond, first *click* on the bond and then move the mouse up and down while simultaneously holding down the left button and the **Alt** key (**Option** key on Macintosh). Speculate why this conformer is preferred. Assuming that this is also the reactive conformer, predict the product of the ene reaction.

^{611.} White, J.D.; Somers, T.C. J. Am. Chem. Soc. 1994, 116, 9912.

The carbonyl ene reaction is catalyzed by Lewis acids.⁶¹² Isobutylene reacted with methyl propiolate at 220°C to give 47% of **741** and 3% of **742**. The presence of aluminum chloride (AlCl₃), however, allowed reaction to occur at 25°C and gave a 61% yield of **741**.⁶¹³ Coordination of the Lewis acid and enophile lowers the LUMO, accelerating the reaction due to the diminished ΔE , just as in the Diels-Alder reaction. The C=O of an aldehyde reacts as an ene. The EtAlCl₂-catalyzed ene reaction of **743** to give **744** in up to 68% yield was part of Paquette and co-workers synthesis of dumsin.⁶¹⁴ Alkenyl ketones also undergo ene reactions. As with the conversion of **743** to **744**, dimethylaluminum chloride (Et_2AlCl) are excellent catalysts for the carbonyl ene reaction and are often the catalyst of choice. When catalyzed by chiral chromium (III) complexes, high asymmetric induction is possible in hetero-ene reactions of this type.⁶¹⁵



The catalyst influences the reaction. The reaction of **745** with formaldehyde gave **746**, but when ZnCl_2 , Me_3Al , AlCl_3 , EtAlCl_2 , and Et_2AlCl were examined, only diethylaluminum chloride (Et₂AlCl) gave good yields (61%).⁶¹⁶ The selectivity in the reaction is due to the more favorable interaction of the aluminum and aryl moieties in the transition state. Good selectivity was also observed in the reaction of *trans*-2-butene with **747**. Anti-selectivity to give **748** was observed when tin chloride (SnCl₄) catalyzed the reaction with either *cis*- or *trans*-2-butene, but syn selectivity (to **749**) was observed when alkyl aluminum catalysts were used (Me₂AlCl, Me₂AlOTf, MeAl(OTf)₂).⁶¹⁷

616. Prashard, M.; Tomesch, J.C.; Shapiro, M.J. Tetrahedron Lett. 1989, 30, 4757.

^{612.} Snider, B.B. Acc. Chem. Res. 1980, 13, 426.

^{613. (}a) Snider, B.B. J. Org. Chem. 1974, 39, 255; (b) Greuter, H.; Bellus, D. Synth. Commun. 1976, 6, 409; (c) Åkermark, B.; Ljungqvist, A. J. Org. Chem. 1978, 43, 4387; (d) Snider, B.B. J. Org. Chem. 1976, 41, 3061; (e) Snider, B.B.; Rodini, D.J.; Conn, R.S.E.; Sealfon, S. J. Am. Chem. Soc. 1979, 101, 5283.

^{614.} Paquette, L.A.; Hu, Y.; Luxenburger, A.; Bishop, R.L. J. Org. Chem. 2007, 72, 209.

^{615.} Ruck, R.T.; Jacobsen, E.N. J. Am. Chem. Soc. 2002, 124, 2882.

^{617.} Mikami, K.; Loh, T.-P.; Nakai, T. Tetrahedron Lett. 1988, 29, 6305.



Imino-ene reactions are known.⁶¹⁸ In one report, lanthanum derivatives catalyzed the reaction. When imine **750** reacted with α -methyl styrene in the presence of Yb(OTf)₃, for example, a 90% yield of the ene product (**751**) was obtained when chlorotrimethylsilane was used as an additive.⁶¹⁹ Catalytic, enantioselective imino-ene reactions of α -imino esters have also been reported.⁶²⁰



11.14.D. Chiral Ene Reactions

The fundamental principles of asymmetric synthesis employed in previous chapters and reactions in this chapter also apply to ene reactions. Chiral additives, chiral auxiliaries or the preparation of chiral templates all lead to good enantioselectivity when applied to the ene reactions. Most chiral ene reactions seem to involve addition of a chiral catalyst or the use of a chiral auxiliary. Oppolzer et al. utilized a chiral auxiliary built into **752** to prepare **753** (90% de)



^{618.} For examples, see (a) Achmatowicz Jr., O.; Pietraszkiewwicz, M. J. Chem. Soc. Chem. Commun. 1976, 484; (b) Borzilleri, R.M.; Weinreb, S.M. Synthesis 1995, 347; (c) Laschat, S.; Grehl, M. Angew. Chem. Int. Ed. 1994, 33, 458; (d) Mikami, K.; Kaneko, M.; Yajima, T. Tetrahedron Lett. 1993, 34, 4841.

619. Yamanaka, M.; Nishida, A.; Nakagawa, M. Org. Lett. 2000, 2, 159.

 ⁽a) Drury, III, W.J.; Ferraris, D.; Cox, C.; Young, B.; Lectka, T. J. Am. Chem. Soc. 1998, 120, 11006; (b) Yao, S.; Fang, X.; Jørgensen, K.A. Chem. Commun. 1998, 2547.

in a synthesis of (+)- α -allokainic acid.⁶²¹ Yamamoto and co-workers used the chiral aluminum catalyst **754** for the intermolecular ene reaction of 1,6-dichlorobenzaldehyde and 2-phenylthio-1-propene to give **755** in 96% yield (65 % ee).⁶²² These catalysts are similar to those used in Section 11.9.B. A similar titanium catalyst (**756**) coupled methylenecyclohexane and methyl glyoxalate to give an 89% yield of **757** (98 % ee). Catalyst **756**⁶²³ was prepared *in situ* by reaction of (*R*)-binaphthyl and bis(diisopropoxytitanium) dibromide [(iPrO)₂TiBr₂]. These few examples are sufficient to illustrate that chiral induction is possible in the ene reaction, using the same techniques that were successful in other pericyclic reactions.



11.15. CONCLUSION

It is clear from the preceding sections that a wide range of cyclic and polycyclic molecules can be prepared by pericyclic reactions. In addition, stereocontrolled syntheses of acyclic molecules are possible via initial cycloaddition followed by cleavage of the ring. The power of these reactions lies in the ability to make carbon bonds with high regioselectivity and stereoselectivity. If the proper chiron or chiral auxiliary is used, high enantioselectivity can be obtained as well. Few synthetic methods allow access to such a large number of natural products, with compatibility with such a large number of functional groups. In succeeding chapters, methods for generating carbon bonds via electrophilic or radical intermediates will be presented.

^{621. (}a) Oppolzer, W.; Robbiani, C.; Bättig, K. *Helv. Chim. Acta* **1980**, *63*, 2015; (b) *Idem Tetrahedron* **1984**, *40*, 1391; (c) Oppolzer, W.; Mirza, S. *Helv. Chim. Acta* **1984**, *67*, 730.

^{622.} Maruoka, K.; Hoshino, Y.; Shirasaka, T.; Yamamoto, H. Tetrahedron Lett. 1988, 29, 3967.

^{623.} Mikami, K.; Terada, M.; Nakai, T. J. Am. Chem. Soc. 1989, 111, 1940.

HOMEWORK

1. Using the tables in this chapter (where possible), particularly Tables 11.1 and 11.2, evaluate the relative rate of reaction for each of the following. For the *faster* reaction, predict the structure, and where data is available predict the regiochemistry and stereochemistry of the major product(s).



2. Give a mechanistic explanation for the following transformation:



3. In section 11.5.A, Boger and co-worker's conversion of tetrazines to diazines via inverse electron demand Diels-Alder reactions was mentioned. Give a mechanistic rationale for the transformation shown, based on this paper, that accounts for formation of the indicated product.



4. Give a mechanistic rationale for the transformation that accounts for one product being formed preferentially and also accounts for the stereochemistry of both products.



5. Explain the different stereochemical outcomes of these reactions:



6. Explain the following transformation:



7. Explain the following transformation:



8. Draw a reasonable transition state for the reaction (sec 11.12.E.ii.) that converted 651 to 652.



9. Give the product for this reaction, and rationalize its formation.



10. Reaction of *N*-tosylimines and allylic sulfonium salts under basic conditions leads to aziridines in this particular work. When the imine shown was treated with the sulfonium salt given in the reaction, a mixture of aziridine and a dihydroazepine were formed. Draw both products and explain formation of the dihydroazepine.



11. Use the tables in this chapter (where possible) to <u>estimate</u> the correct regiochemistry for the products in the following reactions.



12. The macrocyclic compound shown, generated *in situ*, spontaneously reacted to give the indicated product in 63% yield. Explain the formation of this product.



13. In a synthesis of merrilactone A (see *J. Am. Chem. Soc.*, **2002**, *124*, 2080), Danishefsky reports the Diels-Alder reaction gives the cycloadduct shown. This product results from an *exo* approach of the anhydride to the diene, assuming a disrotatory motion of the OTBS group. Although this result is not discussed in the cited reference, offer a suggestion why the Alder endo rule does not predict the major diastereomer.



14. For each of the following reactions give the major product, with correct regiochemistry and stereo-chemistry:







15. In each case, provide a suitable synthesis. Show all intermediate products and all reagents.

16. In each case, devise a retrosynthetic strategy that will lead to a suitable starting material that costs < \$1.00 per g (cite the price and your commercial source). Show the complete synthesis, with all intermediate products and all reagents.











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chapter 12 C^a Disconnect Products: Electrophilic Carbon-Carbon Bond-Forming Reactions

12.1. INTRODUCTION

Chapters 8, 9 and 11 introduced many reactions for making carbon-carbon bonds. Molecules possessing a polarized electrophilic carbon (δ^+) were common in previous chapters, as with the reaction of an alkyl halide or a carbonyl compound reacting with nucleophiles and organometallics in Chapter 8, or with nucleophilic enolate anions in Chapter 9. In section 1.2, disconnection of carbon-carbon bonds generated C^d and C^a fragments and Chapters 8 and 9 focused on C^d fragments. This chapter will focus on reagents and reactions that effectively generate equivalents for a C^a fragment, including substrates possessing a C^{δ^+} unit, and organometallic reagents that give reactions similar to a $C^{\delta+}$ unit. Carbocations obviously correspond to a C^a fragment, but they are reactive intermediate rather than reagents. However, if carbocations can be stabilized, they may be used in ways similar to reagents. This concept will be elaborated later in this chapter. Chapter 2 briefly discussed the structure and nature of carbocations in the context of S_N reactions (sec. 2.6.B). It was clear that the nucleophilic partners reacting with a carbocation were limited to alkenes, alkynes, aromatic rings or compounds containing heteroatoms such as oxygen, sulfur, halogen or nitrogen. Reactions of carbocations with these species will also be discussed in this chapter, with an emphasis on their synthetic utility for making carbon-carbon bonds. Many organometallic reagents (particularly organopalladium and organonickel reagents) generate species that react with nucleophiles, they can be categorized as a C^a equivalent. Therefore, many organometallic reactions are included in this chapter. This chapter will begin with a discussion of free carbocations and exploitation of their molecular rearrangements to generate carbon-carbon bonds and different structures.

12.2. CARBOCATIONS

12.2.A. Cation Stability

A carbocation is an sp² hybridized carbon bearing three substituents, with an empty p orbital perpendicular to the plane of the other atoms (see 1). The sp²-hybridization leads to a trigonal planar geometry. This intermediate has been termed a **carbenium ion** by Olah.¹ It is noted that the old term carbonium ions has been applied to 1, but carbocation is the more useful term

^{1.} Olah, G.A. J. Am. Chem. Soc. 1972, 94, 808.

and will be used in lieu of carbenium ion or carbonium ion.

From the standpoint of reactivity, a carbocation is a transient intermediate that reacts with reagents which are able to provide a pair of electrons to form a new bond to the electrophilic carbon. Formation of this cation is usually the slowest (the rate determining step) in solvolysis or other ionization reactions, and subsequent reactions with a nucleophilic species are fast. The classical S_N1 reaction of *tert*-butyl bromide and aqueous potassium iodide (KI) to give *tert*-butyl iodide is an example where the slowest step (k_1 , sec. 2.6.B).is ionization of the bromide to the planar carbocation **1**. The second reaction, trapping the cation, is the fastest step (k_2). There are many different methods for generating carbocations in addition to the classical ionization, and the rate-determining step can vary with each method. One of the most common methods is to treat an alkene with a suitable acid to generate a carbocation such as **2**. In this reaction the alkene π -bond functions as a base in the presence of the acid, H⁺. The subsequent reaction with the nucleophilic chloride in is similar to the k_2 sequence shown for carbocation **1**, and the overall reaction constitutes an addition reaction. Addition of an acidic reagent (HX) to an alkyne generates a vinyl carbocation intermediate (sec. 2.10.A).

$$\begin{array}{c} R^{1} \\ R^{2} \\ R^{3} \\ R^{3}$$

Formation of 2 raises the issue of regioselectivity in formation of a carbocation. When the terminal alkene shown attacks HCl, the proton can attach to either carbon of the C=C unit to form a primary carbocation or the secondary carbon 2. Reactions of acids HX with alkenes and alkynes give the more stable cation, where the order of stability is $3^{\circ} > 2^{\circ} > 1^{\circ}$ (see below). Dipolar effects (inductive and field) largely explain this order, although hyperconjugation (also see sec. 12.2.C) is also invoked. If we focus of dipolar effects, carbocation 1 can be viewed as a carbon atom with an empty p orbital, and redistribution of electron density towards the positive center (inductive effect) occurs, using electrons from the adjacent bonds, diminishing the net charge and stabilizing the cationic center. When R¹, R², and R³ in 1 are alkyl groups, the carbon atoms of the alkyl substituents release electrons to the positive center. The effect increases with increasing numbers of alkyl groups, leading to greater stability. A 3° cation ($R^1 = R^2 = R^3$) = alkyl in 1) will be more stable than a 2° cation ($R^1 = R^2 = alkyl, R^3 = H$), which is more stable than a 1° cation ($R^1 = R^2 = H$, $R^3 = alkyl$). The least stable cation in this alkyl series will be the methyl cation ($R^1 = R^2 = R^3 = H$ in 3). The energy difference between 1°, 2° and 3° cations is about 11-15 kcal mol⁻¹ (46.1-62.8 kJ mol⁻¹): $\Delta E \ 2^{\circ} \leftrightarrow 3^{\circ} = 11-15$ kcal mol⁻¹ and $\Delta E \ 2^{\circ} \leftrightarrow 1^{\circ}$ = 11-15 kcal mol⁻¹ with $3^{\circ} > 2^{\circ}$ and $2^{\circ} > 1^{\circ}$.² In the transition state leading to carbocation formation, one pathway will generate a 2° cation and another to a 3° cation. The lower energy

 ⁽a) Lossing, F.D.; Semeluk, G.P. Can. J. Chem. 1970, 48, 955; (b) Radom, L.; Pople, J.A.; Schleyer, P.v.R. J. Am. Chem.Soc. 1972, 94, 5935; (c) Arnett, E.M.; Petro, C. Ibid. 1978, 100, 5408.

pathway to the tertiary cation ensures that it will be formed with high selectivity.

If we focus on stabilization of a carbocation by hyperconjugation,³ resonance contributors involving the C–H bonds are invoked, as in resonance contributors 4 and 5 that are drawn for

$\begin{array}{cccc} & \overset{n}{\leftarrow} & \overset{n}{\leftarrow} & \overset{R}{\leftarrow} & \overset{C=C}{\leftarrow} & \overset{n}{\leftarrow} & \overset{n}{\leftarrow} & \overset{R}{\leftarrow} \\ & \overset{H}{} & \overset{H}{} & \overset{H}{} & \overset{H}{} & \overset{H}{} & \overset{H}{} \\ & & 3 & 4 \end{array}$	=ĆH⊕ H 5
---	----------------

carbocation **3**. "*The hyperconjugation concept arisessolelyfromourmodel-buildingprocedures.* When we ask whether hyperconjugation is important in a given situation, we are asking only whether the localized model is adequate

for that situation at the particular level of precision we wish to use, or whether the model must be corrected by including some delocalization in order to get a good enough description."⁴ Using this model, one can draw more resonance contributors for a tertiary carbocation than for a primary or secondary carbocation, leading to greater stability.

Treatment of a secondary or tertiary alcohol with an acid catalyst gives an onium salt (6), which loses water (a good leaving group) to give the cation, and 3° alcohols react faster than 2° alcohols. Heterolytic bond cleavage of a halide or sulfonate ester (C–X, X = Br, Cl, I, OMs, OTs, etc.) in aqueous solvents (solvolysis often requires heating) generates tertiary cations easily, secondary cations with difficulty and primary cations with extreme difficulty. Reaction of amines with nitrous acid (HONO) initially gives a diazoalkane 7, which can generate carbenes when generated under different conditions (see sec. 13.9.B), but in this case 7 readily decompose to a carbocation.⁵

$$\underset{R}{\overset{R}{\xrightarrow{}}} O \xrightarrow{H} \overset{H^+}{\longrightarrow} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} O \xrightarrow{H} \\ R \xrightarrow{} O \xrightarrow{H} \end{array} \right] \xrightarrow{-H_2O} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \end{array} \right] \xrightarrow{R} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{HONO} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}}} \\ R \xrightarrow{} \end{array} \right] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}} \end{array} \end{array} \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}} \end{array} \end{array}] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}} \end{array} \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}} \end{array} \end{array}] \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}} \end{array} \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\xrightarrow{}} \end{array} \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}} \end{array} \end{array}] \xrightarrow{-N_2} \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\overset{R}{\xrightarrow{}} \end{array} \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\xrightarrow{}} \end{array} \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\xrightarrow{}} \end{array} \xrightarrow{-N_2} \xrightarrow{-N_2} \xrightarrow{-N_2} \left[\begin{array}{c} \underset{R}{\xrightarrow{}} \end{array} \xrightarrow{-N_2} \xrightarrow{-N_2} \xrightarrow{-N_2} \xrightarrow{-N_2} \xrightarrow{-N_2} \xrightarrow{$$

Electron releasing substituents (those with a negative or δ - charge, i.e., high electron density) attached to the positive carbon of a carbocation will stabilize the charge, leading to a more stable ion. Both oxygen stabilized cations (8) and sulfur stabilized cations (see 9) are well known. The reaction of aldehydes and ketones with an



acid catalyst (Brønsted-Lowry or Lewis) gives the oxygen-stabilized cation 10 or 11.

^{3.} See Radom, L.; Poppinger, D.; Haddon, R.C. in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions, Vol. 5.*; Wiley: NY, *1976*, pp. 2303-2426.

^{4.} Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry, 3rd Ed.*, HarperCollins, NY, *1987*, p. 68.

 ⁽a) Collins, C.J. Acc. Chem. Res. 1971, 4, 315; (b) Friedman, L. in Carbonium Ions, Vol. II, Olah, G.A.; Schleyer, P.v.R. (Eds.), Wiley, New York, 1970, p 655; (c) Kirmse, W. Angew. Chem. Int. Ed. 1976, 15, 251.

$$\begin{array}{c} O \\ R \\ R \\ R^{1} \end{array} \xrightarrow{H^{+}} \begin{bmatrix} + O \\ -H \\ R \\ R^{1} \end{array} \xrightarrow{O \\ H^{+} \\ R^{1} \end{bmatrix}$$

$$\begin{array}{c} O \\ R \\ R^{1} \\ R^{1} \end{array} \xrightarrow{BF_{3}} \begin{bmatrix} + O \\ -\overline{B}F_{3} \\ R^{1} \\ R^$$

A nitrogen atom that is adjacent to a cation gives substantial stabilization (see resonance form 13), and the actual structure is iminium salt 12, a discreet and well-characterized species with a formal π bond between the carbon and nitrogen. In terms of $\begin{array}{c} R^{1} & R \\ \searrow & N_{+} \\ R^{2} & R \end{array} \xrightarrow{R} \begin{array}{c} R^{1} & R \\ & + \end{array} \xrightarrow{R} \begin{array}{c} N_{+} \\ N_{+} \\ R^{2} & R \end{array} \xrightarrow{R} \begin{array}{c} R^{2} & R \\ R^{2} & R \end{array}$

chemical reactivity, it is useful to consider iminium salts as amino cations (resonance contributor 13) since they react with nucleophiles at the electrophilic carbon, but "amino-cations" such as 8 are not usually invoked in a mechanistic pathway.

The stability provided by an adjacent oxygen atom is apparent in the solvolysis data for substituted primary chloroalkanes.⁶ The oxygen atom is a significant contributor to the increase in the rate of solvolysis of EtOCH₂Cl to form EtOCH₂⁺ when compared to formation of the primary cation derived from 1-chlorobutane (109 versus 1).

On the other hand, moving the EtO group one atom further from the carbon bearing the chlorine has the opposite effect. The electron-withdrawing effect at the α -carbon in EtOCH₂CH₂Cl

destabilizes the resulting carbocation and lowers the rate (0.2)versus 1 for 1-chlorobutane). When a cyclopropyl group is conjugated to a cation (cyclopropylcarbinyl cation 14), that cation is more stable.⁷ The cyclopropane bonds have a relatively high degree of s character (sec. 2.2) that provides



stabilization to a cationic center only when conjugated to that center. The 3D drawing of 14 indicates the relationship of the cyclopropane bonds relative to the positive center.



In general, a heteroatom attached to the positively charged carbon stabilizes $\begin{bmatrix} R^{1} & O^{+} & O^{-}R \\ R^{2} & O^{-}C & O^{+} \\ O & O^{+} & O^{-}R \end{bmatrix}$ a carbocation. If the cationic center bears an electron withdrawing group where the (+)- and δ + centers repel, the carbocation (see 15) is destabilized. Destabilization of a carbocation is usually associated with difficulty in formation of the carbocation. If a π system (not bearing a δ +

center) is conjugated to the cationic center, the positive charge will be dispersed via resonance, diminishing the net charge on the initially formed cationic carbon, and leading to overall stabilization of the carbocation. An allylic cation, for example, disperses the charge over three atoms (see 16). If the cationic carbon is conjugated to a diene (as in 17A and B) the charge is dispersed over five atoms, and in benzylic cations (18A and B) the charge is dispersed over seven atoms including the benzene ring.

^{6. (}a) Reference 4, see p 391; (b) Streitweiser Jr., A. Solvolytic Displacement Reactions, McGraw-Hill, New York, 1962, pp 102-103.

^{7.} (a) Hart, H.; Law, P.A. J. Am. Chem. Soc. 1962, 84, 2462; (b) Hart, H.; Sandri, J.M. Ibid. 1959, 81, 320.



MOLECULAR MODELING: Carbocation Rearrangements

In the presence of acid (silica gel is acidic), the phenylcyclopropane derivative shown loses HCl and yields a substituted indene. The process is believed to involve initial loss of Cl⁻, followed by rearrangement of the carbocation intermediates, **A** to **B** to **C**, and finally loss of H⁺ (see *J. Chem. Soc., Perkin Trans. I 1992*,535, and homework problem 5). Carbocation rearrangements are known to be rapid and reversible, and the indene will only be formed if it is the most stable product.



Build the reactant and use the properties icon to obtain its energy. Click on > to the right of the tab at the top of the screen and select *Continue* to bring up a fresh build panel. Construct the indene product and obtain its energy. Repeat the process to obtain the energy for HCl, and calculate the energy of the overall reaction. Is there a large thermodynamic driving force behind the formation of the indene product? Next, obtain energies for the neutral products resulting from deprotonation of both A and B (isomers of the indene product resulting from deprotonation of C). In terms of overall thermochemistry, is either of these competitive with the substituted indene?

	п	,	$\Delta H^{\ddagger}_{cak}$		
R	(kcal mol ⁻¹)	(kJ_mol ⁻¹)	(kcal_mol ⁻¹)	(kJ_mol ⁻¹)	
Me	950	3979.6	1080	4524.1	
Et	835	3497.8	943	3950.2	
n-Pr	835	3497.8	912	3820.4	
n-Bu	835	3497.8	885	3707.3	
i-Pr	760	3183.6	810	3393.1	
t-Bu	715	2995.1	730	3058.0	
t-Pentyl	685	2869.5	678	2840.1	
Neopentyl	805	3372.2	815	3414.0	
⊳+			1000	4189.0	
□⁺			890	3728.2	
0+			815	3414.0	
()+			782	3275.8	
CH2+			955	4000.5	
➡- CH ₂ ⁺			1105	4628.9	
O+			920	3853.9	
\bigcirc - CH ₂ +	748	3133.4			
N=C - CH2	* 806	3376.3			
MeO - CH	* 660	2764.7			
сі -{ _} сн₂*	766	3208.8			

Table 12.1 Ionization Potential and $\Delta H_{calc}^{\ddagger}$ for Cations

The relative order of carbocation stability is related to the ionization potential of that carbocation, which is experimentally determined by electron bombardment in a mass spectrometer. The ionization potential and relative energies (determined by mass spectrometry) can be used as a measure of the relative order of cation stability.⁸ The lower energy ionization (7.42 eV versus 8.64 eV for *tert*-butyl versus *n*-butyl) represents the more stable cation. As expected, tertiary is lower in energy than secondary, which is lower in energy than primary. Table 12.1⁹ shows the ionization potential for several cations, as determined by mass spectrometry, along with the calculated energy of cations for a chemical ionization pathway ($\Delta H^{\dagger}_{calc}$). The two energy values are not related, however, and cannot be correlated. The mass spectral data obviously exclude solvent effects, which can have a profound influence on the relative stability of the cation. For alkyl cations 3° is more stable than 2°, which is more stable than 1°, as seen in Table 12.1,

^{8.} Deno, N.C. in *Progress in Physical Organic Chemistry, Vol. 2*, Cohen, S.G.; Streitwieser Jr., A.; Taft, R.W. (Eds.), Interscience, New York, *1964*, p 135.

^{9.} Isaacs, N.S. Reactive Intermediates in Organic Chemistry, Wiley, London/New York, 1974, p 151.

which also shows several other types of carbocations, and it is clear that the primary benzyl cation is less stable than the *tert*-butyl cation, but more stable than the secondary isopropyl cation. Electron-releasing groups on the aromatic ring make the benzylic cation more stable, and electron-withdrawing groups make it less stable due to the usual inductive effects (sec. 2.2). The $\Delta H^{\ddagger}_{calc}$ data suggest that the primary allyl cation is less stable than a primary alkyl cation but more stable than methyl. Interestingly, the allylic cation is taken to be only slightly less stable than the benzylic cation, and the propargyl cation is significantly less stable than the allylic cation. The stability of secondary cations derived from cyclic molecules is influenced by the size of the ring, with a stability order C6 > C5 > C4 > C3, and the cyclopentyl cation is about equal in energy to the isopropyl cation.

The relative stability of carbocations can also be measured by determining the ΔH_{rxn} for hydrolysis of alkyl halides. Based on a hydrolysis reaction for which ΔH_{rxn} was measured, the relative stability of various carbocations formed as intermediates from the appropriate chloroalkane.¹⁰ An advantage of this measurement is that solvent effects, which are clearly important in most organic transformations, play a significant role. Cyclic 2° and 3° alkyl cations are more stable than their acyclic counterparts. Tertiary benzylic cations are more stable than the tertiary alkyl cations. An important conclusion is that the order 3° > 2° > 1° applies to all cations, and 3° benzylic > 2° benzylic > 1° benzylic. It is not surprising that a 3° benzylic cation is more stable than the primary benzylic cation, however, which provides an important benchmark for the following order of carbocation stability.

 3° benzylic > 2° benzylic > 3° alkyl > 1° benzylic $\approx 1^{\circ}$ allylic $\approx 2^{\circ}$ alkyl > 1° alkyl > methyl

 Table 12.2
 Relative Rate of Solvolysis of Substituted Chloroalkanes¹¹

$ \begin{array}{c} $						
<u>R</u> ¹	$\underline{\mathbf{R}}^2$	<u>Rate</u>	<u>R</u> ¹	$\underline{\mathbf{R}}^2$	<u>Rate</u>	
Н	Me	1.57x10 ⁻⁶	Н	Ph	0.216	
Me	Me	0.086	Me	Ph	394	
Ph	Me	394	Ph	Ph	19,900	
[Reprinted with permission from Brown, H.C.; Rei, M. J. Am. Chem. Soc 1964, 86, 5008. Copyright © 1964 American Chemical Society.]						

The relative rates of solvolysis for several chloroalkanes (19) provide another practical measure of carbocation stability. The rate of ionization to carbocation 20 is shown in Table 12.2.¹⁰

^{10.} Arnett, E.M.; Hofelich, T.C. J. Am. Chem. Soc. 1983, 105, 2889.

^{11. (}a) Lowry, T.H.; Richardson, K.S. *Mechanism and Theory in Organic Chemistry, 3rd Ed.*, Harper and Row, New York, *1987*, p 385; (b) Brown, H.C.; Rei, M. J. Am. Chem. Soc. *1964*, *86*, 5008.

The more stable cations are formed fastest, leading to a faster reaction since this is the rate determining step. The presence of a second phenyl group in chlorodiphenylmethane led to greater conjugation, greater stability and a significantly higher rate of ionization.

Vinyl carbocations can be generated from a variety of sources, but they are generally less stable than alkyl carbocations.¹² Vinyl cations were first detected by Grob and co-workers in solvolysis reactions of α -aryl vinyl halides,¹³ but have been observed in solvolysis reactions of other alkenyl halides¹⁴ and in electrophilic reactions of alkynes.¹⁵ As with other carbocations, the stability of this intermediate depends upon the groups attached to the positive center. The X-ray structure of a bis(silyl)-stabilized vinyl cation was reported, for example,¹⁶ indicating the special stability of that cation.



With the data presented thus far on carbocation stability, the goal is to estimate the relative stability of common carbocations in order to make a prediction concerning product distribution when there are competitive processes. In a simple example, when alkene 21 is treated with HX, do we obtain product 22 via carbocation 23, or product 25 via carbocation 24? Which is more stable, the primary benzylic cation 24 or the oxygen-stabilized cation 23? The relative energies for various carbocations has been compiled,¹⁷ and Figure 12.1 shows the order of stability based on $D_{(R+H-)}$, which is equivalent to the $\Delta H_f(RH)$ for the reaction $R-H \rightarrow R^+ +$ H⁻. The common carbocations H_3C^+ , MeH_2C^+ , Me_2HC^+ and Me_3C^+ are shown at 313, 271, 252 and 233 kcal mol⁻¹ (1308, 1132, 1053, 974 kJ mol⁻¹), respectively.¹⁷ Note that the vinyl cation (287 kcal mol⁻¹, 1199 kJ mol⁻¹) is less stable than the ethyl cation, but more stable than the methyl cation. Replacing a hydrogen atom in $+CH_3$ with an electron-withdrawing group such as cyano (+CH₂CN, 305 kcal mol⁻¹, 1274 kJ mol⁻¹) is destabilizing, relative to replacing it with a methyl group (the ethyl cation). Replacing hydrogen with an OH (+CH₂OH, 252 kcal mol⁻¹, 1053 kJ mol⁻¹) leads to an ion that is as stable as the secondary isopropyl cation. The primary allylic carbocation (256 kcal mol⁻¹, 1070 kJ mol⁻¹) is almost as stable as a secondary alkyl such as isopropyl cation (252 kcal mol⁻¹, 1053 kJ mol⁻¹). The propargyl cation (271 kcal

^{12.} Dicoordinated Carbocations, Rappoport, Z; Stang, P.J. (Eds), Wiley, New York, 1997.

^{13.} Grob, C.A.; Csapilla, J.; Csch, G. Helv. Chim. Acta 1964, 47, 1590.

^{14.} Hanack, M. Acc. Chem. Res. 1976, 9, 364.

^{15.} Lucchini, V.; Modena, G.; Pasquato, L. in Dicoordinated Carbocations, Rappoport, Z; Stang, P.J. (Eds), Wiley, New York, 1997, p 321.

^{16.} Müller, T.; Juhasz, M.; Reed, C.A. Angew. Chem. Int. Ed. 2004, 43, 1543.

^{17.} Lossing, F.P.; Holmes, J.L. J. Am. Chem. Soc. 1984, 106, 6917.

mol⁻¹, 1132 kJ mol⁻¹) is less stable than the primary allylic. The benzyl carbocation (238 kcal mol⁻¹, 994 kJ mol⁻¹) is almost as stable as the tertiary *tert*-butyl cation (233 kcal mol⁻¹, 974 kJ mol⁻¹), and more stable than the primary allylic and slightly more stable than the secondary allylic carbocation (241 kcal mol⁻¹, 1007 kJ mol⁻¹). Placing the positive charge in a five-membered ring (263 kcal mol⁻¹, 1099 kJ mol⁻¹) is less stable than the cyclohexyl cation (243 kcal mol⁻¹, 1015 kJ mol⁻¹), with the acyclic isopropyl cation in between. Acylium ions are quite stable. The formyl cation (257 kcal mol⁻¹, 1074 kJ mol⁻¹) is about as stable as the primary allyl, and the acetyl cation (230 kcal mol⁻¹, 961 kJ mol⁻¹) is more stable than the tertiary alkyl cation. Note that the amino-cation (iminium ion) is very stable, and the tropylium ion shows the greatest stability in this series. Conversely, the alkyne carbocation is extremely unstable (386 kcal mol⁻¹, 1613 kJ mol⁻¹).



Figure 12.1. Relative Stability of Common Carbocations Based on $D_{(R+-H-)}$, in kcal mol⁻¹.¹⁷ [The data but not the figure is used and reprinted with permission from Lossing, F.P.; Holmes, J.L. *J. Am. Chem. Soc.* **1984**, *106*, 6917. Copyright © 1984 American Chemical Society.]

We can now formulate an answer to the question posed about for **24** versus **23**. A primary benzylic cation (238 kcal mol⁻¹, 994 kJ mol⁻¹) is expected to be less stable than the oxygen-stabilized cation (220 kcal mol⁻¹, 919 kJ mol⁻¹), using Figure 12.1 as a guide. Therefore, **22** is predicted to be the major product. It is likely that a mixture of products will be observed, but the data in Figure 12.1 allows a practical comparison of carbocations that allows one to make reasonable predictions of major and minor products in many cases.

12.2.B. Configurational Instability

As briefly discussed in Section 2.6.B.i and above, carbocations are planar. Therefore, $S_N 1$ type reactions are expected to proceed with racemization since there is little or no facial selectivity in the simple cases. Retention or partial retention and even inversion can occur "if the structure

contains a configuration-holding group, a nucleophilic group which can interact with the carbonium centre".¹⁸ If a tight ion pair is generated, the S_N 1 reaction will show some memory of the departing group since it is in close proximity and partial inversion can occur, which will clearly be solvent dependent. Table 12.3¹⁹ shows the percentage inversion for a series of secondary halides in solvolysis reactions, under a variety of solvolysis conditions. These results indicate that addition of silver ion increases the inversion, presumably via coordination with the halide such that a free cation will not be generated, and the departing bromide is close to the cationic center at the time of the substitution.

Table 12.3% Inversion in S_N1 Type Solvolysis Reactions

<u>Alkyl Halide</u>	<u>Solvent</u>	<u>% Inversion</u>	<u>Alkyl Halide</u>	<u>Solvent</u>	<u>% Inversion</u>		
$H_{C_6H_{13}}$ Br	60% aq EtOH 60% aq EtOH + Ag ⁺	83 97	H ·) - Cl Ph	H ₂ O aq acetone	58 51		
Et V Br C ₆ H ₃	80% aq acetone	60	H CI O ₂ C	$\begin{array}{l} \mathrm{H_2O} \\ \mathrm{H_2O} + \mathrm{Ag^+} \end{array}$	0 61		
[Reprinted with permission from Isaacs, N.S. <i>Reactive Intermediates in Organic Chemistry</i> , Wiley, London/New York, 1974 , p. 119. Copyright © 1974 by John Wiley and Sons, Inc.]							

As a practical matter, reactions of carbocations do not necessarily proceed with complete inversion or retention, but many proceed with partial inversion. It is reasonable, however, to assume that racemization or partial racemization will be the stereochemical outcome of cationic reactions unless there is experimental evidence or literature precedent to support inversion or retention.

12.2.C. Cationic Rearrangements



A second property of carbocations that influences their synthetic utility is their propensity to rearrange to a more stable cation. When alcohol **26** was treated with HCl, two products are possible. The first is the direct $S_N 1$ product **30** (see sec. 2.6.B.ii) that results from trapping the initially formed cation (**27**) with chloride ion (rate constant = k_4). The second product is the rearranged benzylic chloride (**29**). Rearrangement via a 1,2-hydride shift can occur (rate

^{18.} Reference 9, pp 118-119.

^{19.} Reference 9, p 119.

constant = k_2) because the rearrangement product, benzylic cation **28** is more stable than the initially formed **27** (see Fig. 1), and subsequent trapping with chloride ion (rate constant = k_3) gives **29**. In the limiting cases, if $k_2 >> k_4$ only **29** will be observed, whereas only **30** will be observed if $k_4 >> k_2$. In both cases, the initial ionization step (rate constant = k_1) is the slowest (rate-determining) step, and $k_3 \approx k_4$. If the two cation intermediates are close in energy then $k_2 \approx k_4$, and a mixture of products will result or only a modest amount of rearrangement will occur. In many cases, the rearrangement (k_2) proceeds faster than the direct substitution (k_4) and the rearranged product predominates. If the cation and nucleophile are particularly reactive, however, k_4 may be much faster than k_2 . A simplifying *assumption* is that $k_2 > k_4$ in most cases, which not always true, but provides a good working model for relatively simple substrates.

This type of rearrangement is understood by viewing the carbocation intermediate as having an electron deficient p orbital (the positive center), which can gain electron density from an adjacent σ bond. When the σ -bond (C–H) adjacent to the p-orbital is parallel (as in **31**), the σ and p-orbitals can overlap and electron density (i.e. the bond) migrates toward the positive center. The transition state for this process is usually represented as a bridged electrophilic species, **32**. The transformation of **31** to **33** via **32** requires that the hydrogen atom is transported as the electrons in the bond move, and this migration is described as a 1,2-hydride shift of the hydrogen atom to the adjacent carbon to give **33**. This rearrangement occurs when the reaction (**31** \rightarrow

$$\begin{bmatrix} & & & H \\ Me & & & & H \\ H & & & & H \end{bmatrix} \rightarrow \begin{bmatrix} & & H \\ Me & & & & H \end{bmatrix} \rightarrow \begin{bmatrix} & & H \\ Me & & & & H \end{bmatrix} \rightarrow \begin{bmatrix} & & H \\ Me & & & & H \end{bmatrix}$$

33) is exothermic, and if the bond bearing the migrating group can become parallel with the p orbital of the cationic center. In this case, the

more stable benzylic cation is favored over the secondary cation, and the 1,2-hydrogen shift is an exothermic reaction. In general, secondary \rightarrow tertiary, primary \rightarrow secondary, and primary \rightarrow tertiary rearrangements are exothermic reactions, and the rearrangement is facile.

MOLECULAR MODELING: Phenonium Ions

Treatment of the ¹⁴C labeled amine with nitrous acid leads to equal amounts of alcohols **A** and **B**, that is, the label is fully scrambled (see homework problem 8).



This fascinating result may be explained by proposing that the initially-formed diazonium salt decomposes to give a secondary carbocation, which either reacts with water to give **A**, or first rearranges to an equivalent carbocation which then reacts with water to give **B**. Connecting the two secondary carbocations is a bridged carbocation (a *phenonium ion*), a spirocyclic benzenonium

MOLECULAR MODELING: Phenonium Ions, con't.

ion, is able to distribute the positive charge onto the ortho and para ring positions.

Obtain the energy of the secondary carbocation. Is an "open" geometry maintained or has the carbocation collapsed to a phenonium ion? If the carbocation has remained open, then obtain the energy of the phenonium ion. Make sure that the methyl groups are either *cis* or *trans* in both ions. Is the geometry maintained or has the carbocation collapsed into an open geometry? If both ions are stable, which is lower in energy? Could both alcohols be formed from the phenonium ion? If there were a simple 1,2-hydride shift from the initially formed carbocation, what is the structure of the alcohol resulting from that rearrangement?



Why did the hydrogen group in **31** migrate and not the phenyl? First, migration of the phenyl would lead to a significantly less stable primary cation and the reaction would be endothermic. Second, migration of the larger phenyl group may require more energy than the smaller hydrogen. Note that the phenyl group can migrate, and a relatively low-energy phenonium ion such as **34** has been invoked in many aryl migrations.²⁰

In a transition state such as **32**, considerable positive charge can be present and charge dispersal (as in **34**) can facilitate the rearrangement. A lesson from this observation is that careful analysis of a system is required to determine *a priori* which atom will preferentially migrate.

In the absence of electronic effects, smaller alkyl groups will generally migrate before larger ones: $H > Me > CHMe_2 > CMe_3$



It is difficult to give an absolute scale for migratory aptitude since migratory aptitude is inevitably linked to the stability of the cation being formed and the relative energy of the transition state. An example is cation 35, where the larger ethyl group can migrate preferentially (to give 37) rather than the smaller methyl group to give 36. The *p*-methoxyphenyl group will stabilize cation 37 to a greater extent than the *p*-nitrophenyl group stabilizes 36 however. The electron releasing methoxy diminishes the net charge, but the electron-withdrawing nitro group destabilizes the cationic center in 36. In other words, the larger ethyl group can migrate rather than the smaller

^{20. (}a) Lancelot, C.J.; Cram, D.J.; Schleyer, P.v.R. in *Carbonium Ions. Vol. III*, Olah, G.A.; Schleyer, P.v.R. (Eds.), Wiley, New York, *1972*; (b) Reference 4, p. 367.

methyl due to formation of a more stable cation. The analysis for determining which group migrates must take into account both the stability of the cation being formed (relative to that initially available), and the size of the migrating group. If the rearrangement of either hydrogen or methyl will generate a cation of similar stability, the relative size of the migrating group is usually the determining factor and the hydrogen will migrate preferentially.

The presence of an atom or group that can *assist* migration in some way makes it faster, which is another example of neighboring-group participation noted in several previous chapters.²¹ The term σ -**participation** has been used to describe the through-space interaction (sec. 2.2) of an empty p orbital with the electrons in a neighboring bond. In Figure 12.2, **38** represents a transition state for a 1,2-shift that assumes a concerted migration, with ionization of the leaving group (this is effectively a symmetrical bridging transition state).²² The term σ **conjugation** (usually the same as **hyperconjugation**) "implies sideways interaction of orbitals, as in **39** in Figure 12.2. In Figure 12.2, **39a** represents a hyperconjugative interaction of Z with C_a, whereas **39b** represents the case where there is a small amount of σ participation.²² Such neighboringgroup effects can both accelerate the rate of rearrangement and stabilize the cation.



Figure 12.2. σ Conjugation in 1,2-Bond Migrations.



Cationic rearrangements can be highly selective, and several named reactions involve cationic rearrangement. Mundy's monograph is an excellent source that presents many examples of these named reactions.²³ In the Srikrishna et al. synthesis of 6-epijunicedranol, normylataylanone (**43**) was also synthesized,²⁴ when conjugated ketone **40** was treated with boron trifluoride•etherate. Coordination of the carbonyl and Michael-type addition of the exocyclic alkene unit gave tertiary cation **41**. Despite the fact that this is a tertiary cation, it rearranged via a 1,2-alkyl shift

24. Srikrishna, A.; Yelamaggad, C.V.; Kumar, P.P. J. Chem. Soc. Perkin Trans. 1 1999, 2877.

^{21.} Reference 4, pp 429-439.

^{22.} Reference 4, p 431.

^{23.} Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed., Wiley, New York, 2005.

to give spirocyclic carbocation 42. The migration occurred on the face opposite the methyl group, and the enol unit in 42 attacked the tertiary cation from that same face to give ketone 43 selectively, in 60% yield.

Cyclopropylcarbinyl systems (where the cationic carbon is connected directly to a cyclopropyl ring) are subject to ring-expanding cationic rearrangements. In Section 12.2.A, it was noted that the cyclopropyl group imparts special stability to an adjacent cationic, and migration of the strained cyclopropyl bonds in cyclopropylcarbinyl cations such as **14** leads to the less strained homoallylic cation **46**.²⁵ Participation of the cyclopropane ring is apparent in the solvolysis of cyclopropylcarbinyl tosylate (**44**), which occurs 10⁶ times faster than solvolysis of the tosylate of 2-methyl-1-propanol (**45**).²⁶ A cyclobutyl cation (**47**) can also form under these conditions via a ring-expansion reaction (see below). The cyclobutylcarbinyl system (**48**) is less strained than **44**, but also undergoes ring expansion via cyclobutylcarbinyl cation, **49**. Solvolysis of tosylate **48** leads to the cyclopentyl cation (**50**), via ring expansion of **49**.



Cationic rearrangement can be used in other ring expansion reactions, such as the transformation of **51** to **54** upon treatment with acid, albeit in only 9% yield.²⁷ Solvolysis of the tosyl group in **51** produced the unstable primary cation **52**. Rearrangement led to ring expansion to the more stable secondary cation **53**, which lost a proton to give the alkene product (**54**). The overall result was expansion of the eight-membered ring to a nine-membered ring. If bond migration leads to a medium size ring (8-13), the high energy inherent in these rings may inhibit the bond migration to form a larger ring (sec. 6.6.B) and gives poor yields. Despite the fact that a secondary cation is much more stable than a primary cation, the yield of **54** was rather poor. A contributing factor is the ring expansion that generates a nine-membered ring, which is higher in energy than the eight-membered ring precursor.



 ⁽a) Roberts, J.D.; Mazur, R.H. J. Am. Chem.Soc. 1951, 73, 2509; (b) Mazur, R.H.; White, W.N.; Semenow, D.A.; Lee, C.C.; Silver, M.S.; Roberts, J.D. Ibid. 1959, 81, 4390; (c) Brady, S.F.; Ilton, M.A.; Johnson, W.S. Ibid. 1968, 90, 2882; (d) Julia, M.; Mouzin, G.; Descoins, C. C.R. Hebd. Seances Acad. Sci. 1967, 264, 330.

^{26.} Roberts, D.D. J. Org. Chem. 1964, 29, 294; (b) Idem Ibid. 1965, 30, 23.

^{27.} Huisgen, R.; Seidl, G. Tetrahedron 1964, 20, 231.

Carbocations are available from precursors other than halides or sulfonate esters. Treatment of an amine with nitrous acid (HONO) generates an unstable diazonium salt, which decomposes to a transient primary cation. The initially formed cation rearranged to the larger ring cation in what is now known as the **Demjanov rearrangement**.²⁸ In the initially reported reaction, water was present, which trapped the ring-expanded cation as the alcohol.^{29,5ac}

Synthetic applications of this ring expansion generally use the milder reaction conditions associated with alcohol or sulfonate ester precursors. In Fitjer and Mandelt's synthesis of laurene,³⁰ alcohol **55** was heated with *p*-toluenesulfonic acid in benzene to generate cation (**56**), with the positive charge adjacent to a strained four-membered ring. Opening the strained four-membered ring to the lower energy five-membered ring product occurred by a 1,2-alkyl shift to give **57**. Under the reaction conditions, elimination occurred to give a 90% yield of **58** along with 10% of **59**. Note that the stereochemistry of the groups adjacent to the cation can have a significant effect on the migratory aptitude of the groups adjacent to the cationic center.³¹



A relatively simple variation of this reaction is the **Tiffeneau-Demjanov ring expansion**,³²,28c involving treatment of amino alcohols with nitrous acid to produce ring-expanded ketones. The conversion of **60** to a mixture of isomeric ketones in 81% yield is an example.³³ This example illustrates a common problem in ring-expansion reactions in particular and in rearrangements in general, that of regioselectivity. Treatment of **60** with nitrous acid produced cation **61**. Two ring expansion pathways are possible, paths *a* and *b*. The major pathway is path *a*, first giving ring expansion to cation **62** and then a 55% yield of **63**. This pathway also produced 0.7% of the trans ketone. Path *b* led to **64**, which produced 25.6% of ketone **65**. Incorporation of silicon and tin substituents into the molecule mediates the ring expansion.³⁴

^{28. (}a) Demjanov, N.Y.; Lushnikov, M. J. Russ. Phys. Chem. 1903, 35, 26; (b) Idem, Chem. Zentr. 1903, I, 1468;
(c) Smith, P.A.S.; Baer, D.R. Org. React. 1960, 11, 157; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-23.

^{29.} Friedman, L. in Carbonium Ions, Vol. II, Olah, G.A.; Schleyer, P.v.R. (Eds.), Wiley, New York, 1970, p 655.

^{30.} Mandelt, K.; Fitjer, L. Synthesis 1998, 1523.

^{31.} Nikishova, N.G.; Bundel, Yu.G.; Vestn. Mosk. Univ., Ser. 2: Khim 1985, 26, 486 [Chem. Abstr. 104: 167800p, 1986].

 ⁽a) Tiffeneau, M.; Weill, P.; Tchoubar, B. Compt. Rend. 1937, 205, 54; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-93; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 648-649.

^{33.} Parham, W.E.; Roosevelt, C.S. J. Org. Chem. 1972, 37, 1975.

^{34.} Chow, L.; McClure, M.; White, J. Org. Biomol. Chem. 2004, 2, 648.



This ring-expansion process is quite useful when applied to polycyclic systems. Corey and Nozie treated **66** with 40% sulfuric acid, and isolated α -caryophyllene alcohol (**69**).³⁵ The initially formed cyclobutylcarbinyl cation (**67**) rearranged to the cyclopentyl cation (**68**), which was trapped by water to give **70**. Trost and co-workers used ring expansion to generate oxaspiropentane derivatives that were converted to cyclobutane derivatives.^{36,37} In section 8.8.B.ii, oxaspiropentanes such as **70** were prepared by the reaction of ketones and sulfur stabilized cyclopropyl ylids. Treatment of **70** with aqueous tetrafluoroboric acid (HBF₄) gave cation **71**, which rearranged to **72**. Loss of a proton gave the final product, ketone **73**.^{29,28}



Another variation of this ring expansion used sulfur stabilized cations. When aldehyde 74 was treated with trimethylsilyl methyl sulfide and trimethylsilyl triflate, cation 75 was formed and rearranged to the more stable tertiary cation 76. Elimination of the silyl group gave a 59% yield of the *exo*-methylene derivative (77).³⁸ The driving force of this reaction is probably formation of the β -silyl cation in 76. A recent variation treated α -hydroxydithianes with red

^{35. (}a) Corey, E.J.; Nozoe, S. J. Am. Chem. Soc. 1964, 86, 1652; (b) Idem Ibid. 1965, 87, 5733.

^{36. (}a) Trost, B.M. Acc. Chem. Res. 1974, 7, 85; (b) Trost, B.M.; LaRochelle, R.; Bogdanowicz, M.J. Tetrahedron Lett. 1970, 3449.

^{37.} Trost, B.M.; Bogdanowicz, M.J. J. Am. Chem. Soc. 1973, 95, 5311.

^{38.} Tanino, K.; Sato, K.; Kumajima, I. Tetrahedron Lett. 1989, 30, 6551.

HgO and HBF₄, leading to good yields of ring-expanded 1,2-diketones.³⁹



Epoxides react with protonic or Lewis acids to generate cations that are also subject to rearrangement. In Tanino, Kuwajima and co-worker's synthesis of ingenol,⁴⁰ treatment of **78** with trimethylaluminum gave **81** in >80% yield. The epoxide unit reacted with Lewis acid to generate oxonium ion **79**, which rearranged by a 1,2-alkyl shift to give oxygen-stabilized cation **80**. Loss of a proton and protonation of the O-Al unit gave ketone **81**.



A specialized cation rearrangement first observed with bicyclo[2.2.1] systems was the acid catalyzed reaction of camphene hydrochloride (82) to isobornyl chloride (85).⁴¹ The reaction, which proceeded by a 1,2-alkyl shift called the **Wagner-Meerwein rearrangement**,⁴² initially generated bornyl cation 83, but rearrangement to 84 occurred prior to trapping of chloride ion. The term Wagner-Meerwein is often applied to the acid-catalyzed rearrangement of [*m.n.o*]-bicyclo and [*m.n.o*]-tricyclo species, although it applies formally to bicyclo[2.2.1]heptane derivatives.



This reaction has been controversial concerning the structure of norbornyl cations such as 83

^{39.} Ranu, B.C.; Jana, U. J. Org. Chem. 1999, 64, 6380.

^{40.} Tanino, K.; Onuki, K.; Asano, K.; Miyashita, M.; Nakamura, T.; Takahashi, Y.; Kuwajima, I. J. Am. Chem. Soc. 2003, 125, 1498.

^{41. (}a) Wagner, G. J. Russ. Phys. Chem. Soc. 1899, 31, 690; (b) Meerwein, H. Annalen 1914, 405, 129.

 ⁽a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-98; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 678-679.

and **84**.^{43,44} Norbornyl cations have been described in terms of the resonance structures shown in **86**, or as the nonclassical ion **87**.⁴⁵ This view was questioned, primarily by Brown,⁴³ who did not believe that the evidence proved the existence of a bridged intermediate.⁴⁶ Brown suggested that the facile rearrangements could be explained by a series of fast 1,3-Wagner-



Meerwein shifts,⁴⁷ but there is good evidence that the norbornyl cation rearranges with considerable σ -participation.⁴⁸ NMR evidence for the nonclassical ion in super

acids at low temperatures is strong.⁴⁹ Olah is more forceful, stating "it can be concluded that the original views of Winstein⁵⁰ on the nonclassical nature of the norbornyl cation, based on kinetic and stereochemical reactivity, have been substantiated by direct spectroscopic studies of the long-lived ion".⁵¹



The mechanistic controversies have not diminished the synthetically interesting transformations possible with controlled cation rearrangements.⁵² An example is taken from a synthesis of the longipinane skeleton by Joseph-Nathan and co-workers, in which **88** was treated with sulfuric acid to give a 64% yield of the rearranged product **90**.⁵³ The reaction involved rearrangement

- (a) Berson, J.A. in *Molecular Rearrangements, Vol. I*, Mayo, P. (Ed.), New York, p 111; (b) Sargent, G.D. *Quart. Rev. Chem. Soc.* 1966, 20, 301; (c) Olah, G.A. Acc. Chem. Res. 1976, 9, 41; (d) Scheppelle, S.E. Chem. Rev. 1972, 72, 511.
- 46. (a) Brown, H.C. Tetrahedron 1976, 32, 179; (b) Brown, H.C.; Kawakami, J.H.J. Am. Chem. Soc. 1970, 92, 1990.
- 47. Brown, H.C.; Ravindranathan, M. J. Am. Chem. Soc. 1978, 100, 1865.
- 48. (a) Coates, R.M.; Fretz, E.R. J. Am. Chem. Soc. 1977, 99, 297; (b) Brown, H.C.; Ravindranathan, M. Ibid. 1977, 99, 299.
- 49. Olah, G.A. Carbocations and Electrophilic Reactions, Verlag Chemie/Wiley, New York, 1974, pp 80-89.
- 50. (a) Winstein, S. Quart. Rev. Chem. Soc. 1969, 23, 141; (b) Winstein, S.; Trifan, D.S. J. Am. Chem. Soc. 1949, 71, 2953; (c) Idem, Ibid. 1952, 74, 1154.
- 51. (a) Reference 49, p 89; (b) Olah, G.A.; White, A.M.; DeMember, J.R.; Commeyras, A.; Lui, C.Y. J. Am. Chem. Soc. 1970, 92, 4627.
- 52. Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd Ed.*, Wiley, New York, *2005*, pp 678-679.
- 53. Cerda-García-Rojas, C.M.; Flores-Sandoval, C.A.; Román, L.U.; Hernández, J.D.; Joseph-Nathan, P. *Tetrahedron* 2002, 58, 1061.

^{43.} Brown, H.C. The Non-Classical Ion Problem, Plenum, New York, 1977.

^{44.} Story, R.R.; Clark, B.C. in *Carbonium Ions, Vol. III*, Olah, G.A.; Schleyer, P.v.R. (Eds.), Wiley, New York, 1972, p 1007.

of the secondary carbocation 89, with migration of bond 10-11.

Although they are difficult to generalize, several interesting disconnections are possible utilizing cationic rearrangements. Some general examples are



A highly specialized rearrangement is the shift observed during liver microsome-mediated oxidations of aromatic substrates, and during solvolysis of labeled arene oxides,⁵⁴ now called the **NIH shift**.⁵⁵ "In most enzymatic hydroxylations of aromatic substrates the substituent (²H, ³H, or halogen) present at the position of the entering oxygen migrates to either one of the adjacent ring positions."⁵⁶ As observed with an ipso nitration reaction, this shift probably involves an intramolecular hydrogen shift.⁵⁷ A specific example involves enzymatic hydroxylation of chlorobenzene to give **91**. The NIH shift produces **92** and deprotonation, with aromatization, gives the substitution product, 4-chlorophenol.⁵⁵



12.2.D. The Pinacol Rearrangement

and was shown to be applicable to the acid catalyzed rearrangement of most 1,2-diols. The reaction can be generalized to show that 1,2-diols (95) are converted first to a β -hydroxy

^{54. (}a) Daley, J.W.; Hernia, D.M.; Witkop, B. *Experentia* 1972, 28, 1129; (b) Bruice, T.C.; Bruice, P.Y. Acc. Chem. Res. 1976, 9, 378.

^{55.} Guroff, G.; Daly, J.; Jerina, D.; Renson, J.; Witkop, B.; Udenfriend, S. Science 1967, 157, 1524.

^{56.} Jerina, D.M.; Daly, J.W.; Witkop, B. J. Am. Chem. Soc. 1967, 89, 5488.

^{57.} Feldman, K.S.; McDermott, A.; Myhre, P.C. J. Am. Chem. Soc. 1979, 101, 505.

 ⁽a) Fittig, R. Annalen 1860, 114, 54; (b) Collins, C.J. Quart. Rev. Chem. Soc. 1960, 14, 357; (c) Mundy, B.P.; Otzenberger, R.D. J. Chem. Educ. 1971, 48, 431; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-74; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 514-516.

^{59.} Fittig, R. Annalen 1859, 110, 17.

carbocation (96). Rearrangement of pinacol (2.3-dimethyl-2,3-butanediol, for which the reaction is named) to pinacolone (3,3-dimethyl-2-butanone) is the classical example, but the reaction can be done with a variety of 1,2-diols (cyclic and acyclic), utilizing both protonic and Lewis acid initiators. Rearrangement to the more stable 97 (an oxygen-stabilized cation rather than a tertiary alkyl cation, sec. 12.2.A and Fig. 2.1) is followed by loss of a proton to give 98.⁶⁰

$$\begin{array}{c} \text{HO} \quad \text{OH} \\ \text{R} \xrightarrow{} \\ R \\ R \\ \text{P} \\ \text{P} \\ \text{S} \\ \text{P} \\ \text{S} \\ \text{P} \\ \text{S} \\ \text$$

Two important factors are the acid used to initiate the reaction, and the concentration at which the reaction is done.⁶¹ With increasing dilution of the acid as well as the conjugate base, a higher percentage of elimination products are formed rather than the rearrangement product.⁶¹ When Lewis acids are used rather than protonic acids, differences in the reaction pathway are often observed. Treatment of **99** with aqueous perchloric acid gave an 81% yield of **102**, but reaction with boron trifluoride in dichloromethane gave an 88% yield of **105**.⁶² In aqueous media, tertiary cation 100 was formed from 99. Ring expansion to cycloheptyl cation 101 followed by loss of a proton gave ketone 102. Reaction with boron trifluoride in aprotic media proceeded by coordination with the cyclohexanol moiety to form cation 103. Subsequent 1,2-methyl shift (to 104) rather than ring expansion and loss of a proton gave 105. Cation formation can be influenced by rather subtle factors. A double bond in the ring of 99^{63} led to ring expansion with no products such as 105. This reaction is useful for synthesis. An example is the conversion of **106** to **107**,⁶⁴ taken from Pettit and co-worker's synthesis of hydroxyphenstatin. Pinacol rearrangements are useful for the preparation of spirocyclic ketones, when cyclic diol precursors are used. Many spirocyclic compounds^{65,66} are formed by this type of rearrangement. The pinacol rearrangement has been used to construct stereogenic centers adjacent to heterocycles.⁶⁷



^{60.} For reactions of this type, see Larock, R.C. Comprehensive Organic Transformations, 2nd ed., Wiley-VCH, New York, 1999, pp 1281-1282.

- 61. De Lezaeta, M.; Sattar, W.; Svoronos, P.; Karimi, S.; Subramaniam, G. Tetrahedron Lett. 2002, 43, 9307.
- 62. Corey, E.J.; Danheiser, R.L.; Chandrasekaran, S. J. Org. Chem. 1976, 41, 260.
- 63. Bhushan, V.; Chandrasekaran, S. Chem. Lett. 1982, 1537.
- 64. Pettit, G.R.; Lippert III, J.W.; Herald, D.L. J. Org. Chem. 2000, 65, 7438.
- 65. Mundy, B.P.; Kim, Y.; Warnet, R.J. Heterocycles 1983, 20, 1727.
- 66. Krapcho, A.P. Synthesis 1976, 425.
- 67. Shinohara, T.; Suzuki, K. Tetrahedron Lett. 2002, 43, 6937.



The disconnection for these reactions is

$$\overset{R}{\underset{R}{\xrightarrow{}}} \overset{O}{\underset{R}{\xrightarrow{}}} \underset{R}{\overset{R}{\xrightarrow{}}} \underset{R}{\overset{R}{\xrightarrow{}}} \overset{R}{\underset{R}{\xrightarrow{}}} \overset{R}{\underset{R}{\xrightarrow{}}} \overset{R}{\underset{R}{\xrightarrow{}}} \overset{O}{\underset{R}{\xrightarrow{}}} \underset{R}{\overset{O}{\xrightarrow{}}} \overset{O}{\underset{R}{\xrightarrow{}}} \underset{R}{\overset{O}{\xrightarrow{}}} \overset{O}{\underset{R}{\xrightarrow{}}} \overset{O}{\underset{R}{\xrightarrow{$$

Pinacol-like rearrangements are possible from precursors other than diols, especially oxiranes⁶⁸ and allylic alcohols.⁶⁹ In principle, any molecule that generates an intermediate with a positive charge on a carbon α to one bearing an OH group can undergo rearrangement. β -Amino alcohols, for example, rearrange on treatment with nitrous acid via the so-called the *semipinacol rearrangement*,⁷⁰ as do iodohydrins⁷¹ and allylic alcohols, upon treatment with a strong acid that protonates the double bond. An example of the semipinacol rearrangement is taken from Wood and co-worker's synthesis of welwitindolinone A isonitrile,⁷² in which allylic alcohol 108 was treated with sodium hypochlorite in the presence of cerium chloride to give a 78% yield of chloro-ketone 109. Epoxides rearrange when treated with acidic reagents.⁷³ The Meinwald rearrangement⁷⁴ is a related rearrangement induced by the enzyme pigliver esterase.⁷⁵



^{68.} Alarcón, P.; Pardo, M.; Sato, J.L. J. Heterocyclic Chem. 1985, 22, 273.

75. Niwayama, S.; Noguchi, H.; Ohno, M.; Kobayashi, S. Tetrahedron Lett. 1993, 34, 665.

^{69. (}a) Suzuki, K.; Katayama, E.; Tsuchihashi, G. Tetrahedron Lett. 1984, 25, 1817; (b) Idem Ibid. 1983, 24, 4997.

 ⁽a) Pollack, P.I.; Curtin, D.Y. J. Amer. Chem. Soc. 1950, 72, 961 (b) Curtin, D.J.; Pollack, P.I. J. Amer. Chem. Soc. 1951, 73, 992; (c) Curtin, D.Y.; Harris, E.E.; Pollack, P.I. J. Amer. Chem. Soc. 1951, 73, 3453; (d) Curtin, D.Y.; Meislich, E.K. J. Amer. Chem. Soc. 1952, 74, 5905; (e) Curtin, D.Y.; Crew, M.C. J. Amer. Chem. Soc. 1954, 76, 3719. Also see (f) Spivak, C.E.; Harris, F.L. J. Org. Chem. 1972, 37, 2494.

^{71.} Krief, A.; Laboureur, J.L.; Dumont, W.; Labar, D. Bull. Soc. Chim. Fr. 1990, 681.

^{72.} Reisman, S.E.; Ready, J.M.; Hasuoka, A.; Smith, C.J.; Wood, J.L. J. Am. Chem. Soc. 2006, 128, 1448.

 ⁽a) Yandovskii, V.N.; Ershov, B.A. *Russ. Chem. Rev.* 1972, 41, 403, 410; (b) Also see Sudha, R.; Narashimhan, K.M.; K.M.; Saraswathy, V.G.; Sankararaman, S. J. Org. Chem. 1996, 61, 1877; (c) Ranu, B.C.; Jana, U. J. Org. Chem. 1998, 63, 8212.

^{74. (}a) Meinwald, J.; Labana, S.S.; Chadha, M.S.. J. Am. Chem. Soc. 1963, 85, 582; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 420-421.

The term semipinacol rearrangement is applied to the reaction of many substrates, including α -hydroxy aldehydes⁷⁶ epoxy alcohols,⁷⁷ and epoxy ethers,⁷⁸ although the term **pinacol-like rearrangement** is also applied to rearrangement of these substrates. A highly stereoselective rearrangement of 2,3-epoxy alcohols was reported, using the initiator bis(iodozincio)methane.⁷⁹ Pinacol-like rearrangements can be useful in synthesis. In a synthesis of (+)-asteltoxin by Cha and co-worker's,⁸⁰ epoxide **110** was treated with titanium tetrachloride and gave a 96% yield of aldehyde **111**. In another variation, taken from a synthesis of 2-thiocyanaotoneopupukeanane by Uyehara and co-workers,⁸¹ hydroxy ether **112** was treated with tosic acid to give a 96% yield of ketone **113**.



12.3. CARBON-CARBON BOND FORMING REACTIONS OF CARBOCATIONS

There are several synthetically useful and selective carbocation reactions and some classical named reactions involve cationic intermediates. Variations in functional groups, and the reaction conditions used to generate the cation lead to chemoselective transformations that are often highly stereoselective. The intent of this section is to focus attention on the variety of reaction types, and on synthetic applications.

12.3.A. Carbocation Reactions with Alkene Nucleophiles

Alkenes are nucleophiles in reactions with carbocations, donating two electrons from the π bond to form a new bond to one carbon of the C=C. Note that this is the same definition as that for a Lewis base but applied to a carbocation, making the carbocation a Lewis acid in this reaction. Forming this new bond leaves behind a cationic center at the other carbon of the C=C unit (see **115**). Both intermolecular (as in the formation of **115**) and intramolecular (as

- 79. Matsubara, S.; Yamamoto, H.; Oshima, K. Angew. Chem. Int. Ed. 2002, 41, 2837.
- 80. Eom, K.D.; Raman, J.V.; Kim, H.; Cha, J.K. J. Am. Chem. Soc. 2003, 125, 5415.
- 81. Uyehara, T.; Onda, K.; Nozaki, N.; Karikomi, M.; Ueno, M.; Sato, T. Tetrahedron Lett. 2001, 42, 699.

^{76.} For example, see (a) Miller, T.C. J. Org. Chem. 1969, 34, 3829; (b) Schor, L.; Gros, E.G.; Seldes, A.M. J. Chem. Soc. Perkin Trans. 1 1992, 453; (c) Joshi, A.P.; Nayak, U.R.; Dev, S. Tetrahedron 1976, 32, 1423; (d) Benjamin, L.J.; Adamson, G.; Mander, L.N. Heterocycles 1999, 50, 365; (e) Marson, C.M.; Oare, C.A.; McGregor, J.; Walsgrove, T.; Grinter, T.J.; Adams, H. Tetrahedron Lett. 2003, 44, 141.

^{77.} Marson, C.M.; Khan, A.; Porter, R.A.; Cobb, A.J.A., Tetrahedron Lett. 2002, 43, 6637.

^{78.} For a synthesis of (+)-grindelic acid using a pinacol ring expansion involving hydroxy ethers, see Paquette, L.A.; Wang, H.-L. *Tetrahedron Lett.* **1995**, *36*, 6005.

in the formation of **118**) versions are known. The intermolecular process is often plagued by cationic polymerization and/or competitive elimination reactions (E1, sec. 2.9.B), depending of the solvent and relative basicity of the counterion (sec. 2.7). The intramolecular reaction is subject to competing inter- and intramolecular reactions (sec. 6.6.B), but is generally less prone to polymerization although elimination remains a problem. In an intermolecular example, 2-methyl-2-butanol is treated with acid, leading to protonation of the oxygen atom. Loss of



water from this oxonium salt leads to the π bond attacks the cationic center

in an intermolecular reaction to form a new cation (115). In a similar manner, alcohol 116 was the precursor to carbocation 117 when treated with acid. Subsequent intramolecular attack by the alkene moiety on the other side of the same molecule led to carbocation **118**. Formation of 118 is a 6-endo-trig type reaction (see Baldwin's rules, sec. 6.6.A), which can compete with the 5-exo-trig reaction resulting from attack of the cationic center by the other carbon of the alkene moiety. That cyclization process would generate a less stable primary cation so formation of the more stable 118 is favored. Side-reactions are less important in intramolecular cases, so

they are used more commonly in synthesis. The remainder of this section will focus on cationic cyclizations as well as controlled rearrangements.



As seen for **116**, alcohols can generate cations, which then react with an alkene unit elsewhere in the molecule. Reaction of alcohol 119 with 90% sulfuric acid gave 120 as a reactive intermediate that was trapped intramolecularly by the alkene to give the chlorine-stabilized cation 121. Reaction with water led to a chlorohydrin and elimination of HCl gave an enol, which tautomerized to ketone **122** (obtained in 15% yield).⁸²



Alkynes are useful partners in cationic cyclization reactions. Initial reaction of the allylic alcohol moiety in **123** with formic acid gave allyl cation **124**. Subsequent attack by the alkyne moiety across the molecule generated vinyl cation **125**. Trapping the formate anion generated a formate enol ester (C=C-OCHO) and hydrolysis liberated the final ketone product 126, which Lansbury and Serelis converted to damsinic acid.83

^{82.} Lansbury, P.T.; Nienhouse, E.J. J. Am. Chem. Soc. 1966, 88, 4290.

^{83.} Lansbury, P.T.; Serelis, A.K. Tetrahedron Lett. 1978, 1909.



The Johnson polyene cyclization⁸⁴ (the Stork-Eschenmoser postulate), described in Section 10.8.A, is an example of a *cascade cationic cyclization*. Polyenes such as squalene are expected to assume a steroid-like conformation in the lowest energy conformation (sec. 1.5.E), based on the biogenetic preparation of cholesterol from squalene.⁸⁵ In practice, treatment of polyenes with acid led to a very low yield of tri- or tetracyclic products, giving instead significant amounts of polymeric material. Diligent work over many years prevailed, however, and Johnson and his co-workers solved the many problems (as described in sec. 10.8.A) to make this reaction an excellent and efficient synthetic route to di-, tri- and tetracyclic molecules. One of the later examples of polyene cyclization uses an allyl silane to quench the cyclization process.⁸⁶ Initial reaction of the dioxolane unit in of 127 with tin tetrachloride (SnCl₄) led to a 23% yield of tetracyclic 128a (2:3 α : β 17-vinyl) and 11% of 128b (1:1 α : β 17-vinyl). In this case, the Lewis acid partially cleaved the ketal protecting group (sec. 7.3.B.i) during the cation initiation process. The cyclization generated the stereochemical centers at the ring junctures with high selectivity but provided little stereocontrol for the final reaction, which gave a mixture of 17α and 17β-vinyl groups. Better results were obtained by use of a cyclopentenyl moiety rather than a dioxolane unit to conformationally anchor the cationic cyclization process and incorporating an alkyne to terminate that process (with a vinyl cation that was converted to a ketone).⁸⁷



Cyclization can be accomplished when there are heteroatom substituents. Reaction of amidediene **129** with paraformaldehyde and formic acid generated iminium salt **130**. Cationic cyclization (the formate anion is the nucleophilic trapping agent) generated the perhydroisoquinoline **131**.⁸⁸ A related cyclization procedure that involves *N*-acyl iminium

 ⁽a) Johnson, W.S. Acc. Chem. Res. 1968, 1, 1; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 348-349.

^{85.} Clayton, R.B. Quart. Rev. Chem. Soc. 1965, 19, 168.

^{86.} Johnson, W.S.; Chen, Y.-Q., Kellogg, M.S. J. Am. Chem. Soc. 1983, 105, 6653.

^{87.} Gravestock, M.B.; Johnson, W.S.; McCarry, B.E.; Parry, R.J.; Ratcliffe, B.E. J. Am. Chem. Soc. 1978, 100, 4274.

^{88.} Kano, S.; Yokomatsu, T.; Yuasa, Y.; Shibuya, S. Tetrahedron Lett. 1983, 24, 1813.

intermediates was developed by Speckamp and Hiemstra,⁸⁹ and has been used for the preparation of alkaloids.⁹⁰ This route has been used to prepare chiral heterocycles.⁹¹ In this reaction an *N*-alkenyl, ω -hydroxy (or alkoxy) lactam such as **132** is treated with formic acid, generating the acyl iminium salt **133**. Subsequent alkene cyclization led to **134**⁹² and trapping with formate (an S_N1 reaction) gave the final indolizidine product **135**. Selective reduction of an imide precursor gave the ethoxy lactam (**132**) required for generating the iminium salt (sec. 4.4.A). The reaction appears to be under kinetic control and proceeds via a chair-like transition state (**133**), where the incoming nucleophile (HCO₂⁻) and the carbon being attacked are antiperiplanar. Acyl iminium ions have become useful synthetic intermediates.⁹³ Speckamp and Wijnberg applied this method to the synthesis of mesembrine.⁹⁴ Overman and Robichaud used a variation of this reaction to a synthesis of geissoschizine.⁹⁵ Initial reaction of **136** with paraformaldehyde and camphorsulfonic acid generated iminium salt **137** *in situ*. Reaction of the vinyl silane moiety with NaF led to addition of the C=C to the iminium salt (sec. 7.3.A.i). The alkylidene product (**138**) was produced in 80% yield as a 9.1:1 mixture of (*Z/E*) isomers.



- 89. Speckamp, W.N.; Hiemstra, H. Tetrahedron 1985, 41, 4367.
- (a) Speckamp, W.N.; Hiemstra, H. Tetrahedron 1985, 41, 4367; (b) Speckamp, W.N.; DeBoer, J.J.J. J. R. Neth. Chem. Soc. 1983, 102, 405 [Chem. Abstr. 100: 51412b, 1984].
- 91. Royer, J.; Bonin, M.; Micouin, L. Chem. Rev. 2004, 104, 2311.
- 92. Speckamp, W.N. Rec. Trav. Chim. Pay-Bas 1981, 100, 345.
- 93. Maryanoff, B.E.; Zhang, H.-C.; Cohen, J.H.; Turchi, I.H.; Maryanoff, C.A. Chem. Rev. 2004, 104, 1431.
- 94. Wijnberg, J.B.P.A.; Speckamp, W.N. Tetrahedron Lett. 1975, 3963.
- 95. Overman, L.E.; Robichaud, A.J. J. Am. Chem. Soc. 1989, 111, 300.

A similar cyclization procedure uses *C*-acylnitrilium ions for the synthesis of heterocyclic compounds.⁹⁶ A typical example treated isonitrile **139** with trimethylacetyl chloride to give **140**.⁹⁷ Subsequent treatment with CF₃SO₃Ag (silver trifluoromethanesulfonate) gave an intermediate *C*-acylnitrilium ion (**141**), which cyclized to give dihydroisoquinoline derivative **142** in 82% yield. Livinghouse and co-workers used this strategy to synthesize dendrobine,⁹⁸ where a key step was the coupling of **143** with **144** in the presence of molecular sieves. Subsequent treatment with silver tetrafluoroborate gave an 88% yield of **145**. Stevens and Kenney had previously reported a mercury(II) nitrate-mediated Ritter coupling that involved formation of an organomercury compound.⁹⁹ Addition to an isonitrile gave an iminium salt that could be reduced. Although this method did not involve an acylnitrilium ion, it is related to this chemistry.



Other cationic precursors are available. Aldehydes and ketones are protonated under various conditions to form an oxo-stabilized cation (⁺C–OH), which is then attacked by an alkene to form a new carbon-carbon bond. In section 3.2.B.ii, it was shown that oxidation of acid-sensitive alcohols with PCC could be accompanied by secondary reactions. The oxidation of citronellol (146) with PCC not only gave the expected aldehyde, but the aldehyde oxygen was protonated to give 147.¹⁰⁰ Once formed, this oxo-cation is attacked by the adjacent π -bond of the alkene to form cation 148. Elimination to an alkene (E1, sec. 2.9.B), and oxidation to the ketone under the reaction conditions leads to the final product, isopulegone (149).

^{96.} Livinghouse, T. Tetrahedron 1999, 55, 9947.

^{97.} Westling, M.; Livinghouse, T. Tetrahedron Lett. 1985, 26, 5389.

^{98.} Lee, C.H.; Westling, M.; Livinghouse, T.; Williams, A.C. J. Am. Chem. Soc. 1992, 114, 4089.

^{99.} Stevens, R.V.; Kenney, P.M. J. Chem. Soc. Chem. Commun. 1983, 384.

 ⁽a) Corey, E.J.; Boger, D.L. *Tetrahedron Lett.* 1978, 2461; (b) Corey, E.J.; Ensley, H.E.; Suggs, J.W. J. Org. *Chem.* 1976, 41, 380.



A variety of disconnections are possible utilizing intramolecular cationic reactions. A few of the more useful are



12.3.B. Koch-Haaf Carbonylation¹⁰¹

When an alcohol is heated in strong acid, in the presence of carbon monoxide (CO), the initially generated cation traps carbon monoxide to give a carboxylic acid in what is known as the **Koch-Haaf carbonylation**. As with any other carbocation intermediate, rearrangement can occur, usually prior to reaction with carbon monoxide. Reaction of **150** with aqueous sulfuric acid initially gave cation **151**. In the presence of carbon monoxide (generated *in situ* from formic acid and sulfuric acid), acylium ion **152** was formed and reaction with water gave the carboxylic acid (**153**) in 90% yield. Similar treatment of alkenes with these reagents also gave carboxylic acids, but the yields were usually poorer. In most cases, using a sulfuric-formic acid mixture to generate carbon monoxide is more efficient than bubbling in carbon monoxide gas. Lactones are formed when diols are treated with carbon monoxide and acid.¹⁰²



The Koch-Haaf disconnection is

$$R_2HC - CO_2H \implies R_2HC - OH$$

^{101. (}a) Koch, H. Brennst. Chem. 1955, 36, 321 [Chem. Abstr. 50:6019g 1956]; (b) Koch, H.; Haaf, W. Annalen 1958, 618, 251; (c) Möller, K.E. Brennst. Chem. 1966, 47, 10 [Chem. Abstr. 64:12563b 1966]; (d) The Merck Index, 14th ed.,Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-52; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr. F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 368-369.244-245 (see p 328).

^{102.} Takahashi, Y.; Yoneda, N.; Nagai, H. Chem. Lett. 1982, 1187.

12.3.C. Nazarov Cyclization¹⁰³

Divinyl ketones are useful precursors for the synthesis of cyclopentenones. In a typical example, reaction of a divinyl alkyne such as **154** with aqueous acid generated a conjugated ketone (**155**), via hydration of an intermediate vinyl cation.^{103b} Subsequent treatment with a mixture of phosphoric and formic acids led to a new, oxygen-stabilized carbocation (**155**) that reacted with the adjacent alkene (a cyclization reaction) to form **157**. Elimination led to the conjugated ketone (**158**).^{103b} This cationic ring-closing reaction is called the **Nazarov cyclization**.^{103,104104} Several methods are available for the preparation of the bis(conjugated) ketones required for this reaction. Most involve coupling a vinyl carbanion equivalent with a conjugated carbonyl. The strongly acidic conditions used in the reaction that gave **158** are not required for the cyclization.¹⁰⁵ and Lewis acids such as tin chloride (SnCl₄) or iodotrimethylsilane can be used in a Nazarov cyclization. A synthetic example, taken from Danishefsky and co-worker's synthesis of (–)-scabronine G, involved treatment of **159** with ferric chloride give the cyclopentenone unit in **160**, in 72% yield.¹⁰⁶



The cyclization can be accomplished under even milder conditions by incorporating a stabilizing



group on the alkene. Both silane and stannane derivatives have been prepared. Cyclization of **161** gave **162**, for example, but both the temperature and the nature of the Lewis acid had a significant effect on the reaction.¹⁰⁷ Ferric chloride (FeCl₃) gave the best yield of the Nazarov product (**162**) in this study. Vinyl

- 106. Waters, S.P.; Tian, Y.; Li, Y.-M.; Danishefsky, S J. J. Am. Chem. Soc. 2005, 127, 13514.
- 107. Denmark, S.E.; Jones, T.K. J. Am. Chem. Soc. 1982, 104, 2642.

^{103. (}a) Nazarov, I.N.; Torgov, I.B.; Terekhova, L.N. *Izv. Akad. Nauk. SSSR otd. Khim. Nauk* 1942, 200; (b) Braude, E.A.; Forbes, W.F. J. Chem. Soc. 1953, 2208.

^{104.} For reactions of this type, see reference 79, p 1308. Also see (a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-64; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 448-449.

^{105.} Marino, J.P.; Linderman, R.J. J. Org. Chem. 1981, 46, 3696.

silane cyclization can proceed with modest diastereoselectivity.¹⁰⁸ West and Giese¹⁰⁹ showed that a normal Lewis acid catalyzed Nazarov cyclization in the presence of triethylsilane was accompanied by formation of a reduced product. When **163** was treated with BF₃•OEt₂ and two equivalents of triethylsilane, followed by 1N HCl in a second step, a 71% yield of **164** was obtained along with 14% of **165**.¹⁰⁹ Other variations are known. Vinyl stannanes are good Nazarov precursors, for example, generating cyclopentenone derivatives.¹¹⁰



The Nazarov disconnection is



Note that Harmata and Lee reported a retro-Nazarov reaction.¹¹¹ When **166** was treated with triethylamine in trifluoroethanol, for example, a 65% yield of **167** was obtained along with 9% of **168**. This reaction appears to be a good route to dienones.



12.3.D. Noyori Annulation

Another synthetically useful carbon bond-forming reaction is related to the Nazarov cyclzation, but involves reaction of diiron nonacarbonyl (see Sect. 12.10) with halocarbonyl compounds. Noyori and co-workers found that α, α' -dibromoketones (169) react with diiron nonacarbonyl [Fe₂(CO)₉] to give an iron stabilized alkoxy zwitterion (170). The intermediate π -allyl iron species reacts with alkenes in a stepwise manner (initially producing 171) to give cyclic ketones such as 172,¹¹² and the product is equivalent to the product of a [3+2]-cycloaddition with an

^{108.} Jones, T.K.; Denmark, S.E. Helv. Chim. Acta 1983, 66, 2397.

^{109.} Giese, S.; West, F.G. Tetrahedron 2000, 56, 10221.

^{110.} Peel, M.R.; Johnson, C.R. Tetrahedron Lett. 1986, 27, 5947.

^{111.} Harmata, M.; Lee, D.R. J. Am. Chem. Soc. 2002, 124, 14328.

 ^{112. (}a) Noyori, R.; Yokoyama, K; Hayakawa, Y. J. Am. Chem. Soc. 1973, 95, 2722; (b) Idem Ibid. 1978, 100, 1791; (c) Noyori, R. Acc. Chem. Res. 1979, 12, 61.

alkene (sec. 11.11). This cyclization method is now known as **Noyori annulation**,¹¹³ but is clearly related to the Nazarov cyclization just discussed. Enamines can react with **169**, but the initially formed enamino ketone product eliminates the amino group to form cyclopentanone derivatives.¹¹⁴ Intermediates such as **170** may actually exist as cations bound to a metal rather than as the alkoxide-iron structures shown.^{112b-d} It is also noted that $Zn/B(OEt)_3$ is also an effective reagent and is a less toxic and less expensive alternative to Fe₂(CO)₉.^{112e}



Dienes react to give cycloheptenones, as in the reaction sequence initiated by the reaction of **173** with $Fe_2(CO)_9$ to give **174**. In the presence of 2,3-dimethyl-1,3-butadiene generates the cycloheptenone derivative (**175**) in 55% yield.¹¹⁵ This variation is the formal equivalent of a [4+3]-cycloaddition, and furan or pyrrole can be used as the diene component.¹¹⁴ Furan is a useful partner in this annulation, reacting with **176** to produce **177** in a synthesis of showdomycin.¹¹⁶ Cycloadduct **177** was isolated after reduction of the bromide moieties with Zn/Cu (sec. 4.9.G) in the initially formed adduct. A similar strategy was used for a synthesis of nezukone.¹¹⁷ *N*-Boc-pyrroles¹¹⁸ cyclize to 8-azabicyclo[3.2.1]octan-3-one derivatives using diethyl zinc to initialize the Noyori annulation.



Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 464-465.

- 115. Takaya, M.; Makino, S.; Hayakawa, Y.; Noyori, R. J. Am. Chem. Soc. 1978, 100, 1765.
- 116. Sato, T.; Ito, R.; Hayakawa, Y.; Noyori, R. Tetrahedron Lett. 1978, 1829.
- (a) Hayakawa, Y.; Sakai, M.; Noyori, R. Chem. Lett. 1975, 509; (b) Hayakawa, Y.; Baba, Y.; Makino, S.; Noyori, R. J. Am. Chem. Soc. 1978, 100, 1786.
- 118. Paparin, J.-L.; Crévisy, C.; Grée, R. Tetrahedron Lett. 2000, 41, 2343.

^{114. (}a) Hayakawa, Y.; Yokoyama, K.; Noyori, R. J. Am. Chem. Soc. 1978,100, 1799; (b) see J. Am. Chem. Soc. 1972, 94, 3201; (c) J. Am. Chem. Soc. 1972, 94, 1373, 3201, 3940, 6213, 7832; (d) Angew. Chem. Int. Ed. 1973, 12, 239; (e) Tetrahedron Lett. 1975, 4487.

The Noyori annulation disconnections are



12.3.E. The Prins Reaction¹¹⁹

Formaldehyde can be coupled to an alkene in the presence of an acid to give a diol (178) or a 1,3-dioxane derivative (180) in what is known as the **Prins reaction**.¹¹⁹ Allylic alcohols such as 179 can also be produced in this reaction. The use of alternative acids, including Lewis acids, may lead to other products. In a synthesis of (–)-centrolobine by Rychnovsky and co-workers,¹²⁰ α -acetoxy ether 181 was treated with tin bromide, to give an 84% yield of cyclized product 182 as the bromide. This cyclization proceeded without side-chain exchange or partial racemization by reversible 2-oxonia Cope rearrangement, which are potential problems occur during Prins cyclization. Prins cyclization reactions also occur using cyclic α , β -unsaturated acetals with allylsilane nucleophiles, inside Lewis acidic micelles in water.¹²¹



 $\begin{array}{c} \stackrel{OH \quad OH}{\underset{R}{\longleftarrow}} \xrightarrow{R} \\ \end{array}$

The examples in this section demonstrate that stable cations can be generated and trapped with alkenes, alcohols or carbonyl derivatives. The resulting reaction products contain new carbon-carbon bonds, often produced with controllable and predictable stereo- and regiochemistry.

⁽a) Prins, H.J. Chem. Weekblad 1919, 16, 64, 1072, 1510 [Chem. Abstr. 13: 3155, 1919] and [Chem. Abstr. 14: 1119, 1920]; (b) Arundale, R.; Mikeska, L.A. Chem. Rev. 1952, 51, 505; (c) Adams, D. R.; Bhatnagar, S. P. Synthesis 1977, 661; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-76; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 532-533.

^{120.} Marumoto, S.; Jaber, J.J.; Vitale, J.P.; Rychnovsky, S.D. Org. Lett. 2002, 4, 3919.

^{121.} Aubele, D.L.; Lee, C.A.; Floreancing, P.E. Org. Lett. 2003, 5, 4521.

12.4. FRIEDEL-CRAFTS REACTIONS

This section discusses a specialized reaction of carbocations and a nucleophilic species. In this section, however, the nucleophilic species is an aromatic ring and reaction with a carbocation generates a Wheland-type intermediate (sec. 2.11.A) that leads to a substituted aromatic system. Known as Friedel-Crafts reactions, they are among the most important reactions in Organic chemistry.

12.4.A. Electrophilic Aromatic Substitution

In chapter 2, electrophilic reagents such as the bromonium ion $[Br^+$, generated by the reaction of bromine (Br_2) and aluminum bromide $(AlBr_3)]$, were shown to react with benzene to give a resonance-stabilized cation called a **Wheland intermediate** (sec. 2.11). Loss of a proton from the Wheland intermediate and concomitant aromatization gave bromobenzene. In a similar manner, section 2.11 discussed formation of several substituted benzene derivatives.¹²² This section will discuss electrophilic substitution reactions of aromatic derivatives that form carbon-carbon bonds, and the Wheland intermediate will be observed again.¹²²

In section 2.11, we saw that the presence of electron-releasing groups of the aromatic ring (alkyl, oxygen, nitrogen, sulfur, aryl) led to ortho- and para-substituted derivatives as the major products. All of these substituents are electron rich, and most contain a δ - dipole or have a (-) charge adjacent to the aromatic ring. These groups are known as **activating substituents** because they increase the rate of substitution relative to benzene.¹²² The rate of nitration of anisole was 9.7 x 10⁶ times faster than the rate of nitration of benzene, for example. As discussed in Section 2.11, both ortho and para products can be formed from aromatic molecules containing an electron-releasing group. This selectivity is due to formation of a Wheland intermediate that has a positive charge in the ring, adjacent to a substituent that has a (-) or δ - center (including an electron releasing alkyl group). Such an intermediate is more stable, which favors formation of the ortho- and para-substituted products. For this reason, activating substituents are commonly called ortho/para directors. Reaction of anisole with nitric acid/ sulfuric acid mixture, for example, gave 44% of the ortho product (2-nitroanisole), 56% of the para product (4-nitroanisole) and < 1% of the meta product 3-nitroanisole.¹²³ Meta substituent.

Electron-withdrawing groups (NO₂, C=O, SO₂R, SO₃R, NR₄⁺) all have a (+) charge or δ + dipole adjacent to the aromatic ring, and show the opposite effect when compared with activating substituents. They slow the rate of reaction relative to benzene (they are called **deactivating groups**), and are meta directors because the meta product is usually the major product. With a deactivating (electron withdrawing) substituent on an aromatic ring, attack at either the ortho

^{122.} Stock, L.M. Aromatic Substitution Reactions, Prentice-Hall, Englewood Cliffs, New Jersey, 1968.

^{123.} Reference 122, p 43.

or the para position will generate a Wheland intermediate that has a (+)-charge adjacent to a (+) or a δ + center. The proximity of the two like charges destabilizes that intermediate and it is more difficult to form, so ortho/para substitution is slower when compared to benzene. Substitution at the meta position generates a Wheland intermediate that does not have the cationic center adjacent to the (+) or δ + center, and although it is not particularly stabilized it is not strongly destabilized. Therefore, meta substitution is the major product. Selectivity for the meta product is usually good. Nitration of nitrobenzene with a mixture of nitric and sulfuric acid gave 1,3-dinitrobenzene in 94% yield with only 6% of the ortho product and < 1% of the para product.¹²² The ortho/para or meta selectivity is illustrated in Table 12.4,^{124,122} which shows the relative of ortho, meta and para products observed in the nitration of aromatic derivatives. In accord with the concept of activating and deactivating substituents, the presence of heteroatoms in the aromatic ring have a strong influence on electrophilic aromatic substitution reactions. Electron-rich aromatic rings such as phenols and aryl ethers react very well. Such activated heteroaromatic compounds include pyrrole, furan or thiophene. However, pyridine has an electron pair external to the ring, which is deactivating, so it reacts more slowly. This simple analysis is consistent with the order of reactivity shown, with pyrrole being the most reactive and pyridine being rather unreactive to electrophilic aromatic substitution:¹²⁵ In part, pyridine and related compounds are bases, and they react with the added Lewis acid (via the one electron pair) to divert or even suppress formation of a Wheland intermediate.

 Table 12.4
 Regiochemical Preferences for Nitration of Aromatic Substrates

$\xrightarrow{X} \xrightarrow{HNO_3, H_2SO_4} \xrightarrow{X} NO_2$							
	NI	TRATIO	N		Ν	ITRATIC	DN
X	<u>%_ortho</u>	<u>% meta</u>	% para	<u>X</u>	<u>%_ortho</u>	% <u>meta</u>	% para
OMe	44	<1	56	Cl	30	1	69
NHAc	20	<1	80	Br	37	1	62
Ph	69	<1	31	CO ₂ H	22	76	2
Me	59	4	37	NO ₂	6	94	<1
F	9	<1	91	NMe ₃ ⁺	<1	89	11
[Leon M. Stock, <i>AROMATIC SUBSTITUTION REACTIONS</i> , © 1968 , p. 44. Reprinted by permission of Prentice Hall, Englewood Cliffs, New Jersey.]							

^{124.} Reference 122, p 44.

^{125.} Reference 129, p 42.

12.4.B. Friedel-Crafts Alkylation



12.4.B.i. Alkyl Cations and Regioselectivity. This chapter deals with reactions that form carbon-carbon bonds via carbocation intermediates, including coupling reactions with aromatic rings. An aromatic compound will

react with a carbocation intermediate (also see section 12.4.A) to form a Wheland intermediate (namely, **183**). Subsequent loss of a proton, with concomitant aromatization, completes the substitution reaction to form arene **184** via electrophilic aromatic substitution. The reaction with an alkyl carbocation is called **Friedel-Crafts alkylation**,¹²⁶ first reported by Friedel and Crafts in 1877.¹²⁷ The carbocation required for this reaction can be generated from an alkene, an alcohol or an alkyl halide.

In chapter 2, solvolysis reactions of alkyl halides in aqueous or highly protic media were shown to form carbocations that typically lead to $S_N 1$ or E1 products. Such reactions were limited to tertiary and secondary halides, due to the energy demands for the initial ionization. Alkyl halides also react

$$R^{2} \xrightarrow[R^{3}]{I} \xrightarrow{AlCl_{3}} R^{2} \xrightarrow[R^{3}]{C^{+}} AlCl_{4} \xrightarrow{R^{1}} R^{3}$$

$$R^{2} \xrightarrow{R^{1}} R^{3}$$

$$R^{3}$$

$$185$$

with Lewis acids, but tertiary, secondary or primary halides react to form tertiary, secondary or primary carbocations (**185**). Formation of a primary cation (**185**, $R^1=R^2=H$, $R^3=$ alkyl) is somewhat slower and is, of course, subject to rearrangement. As a result, primary alkyl derivatives are rarely observed under these conditions. The extent of rearrangement from primary and secondary cations depends on the reaction conditions, the strength of the nucleophile, and the



h nature of the cation. Reaction of benzene and 1-phenyl-2-chloropropane (**186**), for Me example, gave 60% of **187**,¹²⁸ with little rearrangement to the benzylic cation. This result suggests that the initially formed

cation can be trapped very rapidly, possibly via a tight ion pair. In this particular case, the solvent (carbon disulfide, CS_2) played a major role in minimizing solvent separation of the ions.

Alkyl fluorides are the most reactive of the alkyl halides. All the boron trihalides catalyze the reaction of alkyl fluorides and benzene, although they are ineffective catalysts for the analogous

^{126.} For reactions of this type, see reference 79, pp 129-133. Also see (a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-34; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 256-257.

 ^{127. (}a) Friedel, C.; Crafts, J.M. Compt. Rend. 1877, 84, 1392, 1450; (b) Price, C.C. Org. React. 1946, 3, 1; (c) Gore, P. Chem. Rev. 1955, 55, 229; (d) Baddeley, G. Quart. Rev. Chem. Soc. 1954, 8, 355.

^{128.} Masuda, S.; Nakajima, T.; Suga, S. Bull. Chem. Soc. Jpn. 1983, 56, 1089.

reaction with alkyl chlorides and alkyl bromides.¹²⁹ In a reaction with mixed halides, the C–F bond reacts faster than the C–Cl, C–Br or C–I bonds.¹³⁰ This is consistent with the observed order of reactivity for alkyl halides with aluminum chloride (AlCl₃):

$$R-F > R-Cl > R-Br > R-I^{131}$$

Table 12.5The ortho Effect and ortho-para Substitution in Friedel-Crafts Reactions of
Anisole and Toluene

$\begin{array}{ c c c c c c }\hline R^1 & \hline R & \hline R^1 & \hline R & \hline R^1 & \hline R & $								
<u>R</u> 1	<u>R–X</u>	<u>Catalyst</u>	<u>Solvent</u>	<u>Time (min)</u>	<u>Temp. (°C)</u>	<u>%_ortho</u>	<u>% meta</u>	% para
OMe	MeF	BF ₃	anisole	30	25	75	<1	25
OMe	MeF	BF ₃	nitromethane	15	25	55	<1	45
Me	MeF	BF ₃	anisole	30	25	54	18	28
OMe	MeCl	AlCl ₃	nitromethane	5	25	68	2	30
Me	MeCl	AlCl ₃	nitromethane	52	17	31		
OMe	MeBr	AlCl ₃	nitromethane	30	25	67	2	31
Me	MeBr	AlCl ₃	nitromethane	54	17	29		
OMe	MeI	AlCl ₃	nitromethane	60	25	67	<1	32
Me	MeI	AlCl ₃	nitromethane	57	12	31		
[Reprin Copyrig	[Reprinted with permission from Olah, G.A.; Olah, J.A.; Ohyama, T. J. Am. Chem. Soc. 1984, 106, 5284. Copyright © 1984 American Chemical Society.]							

As with other electrophilic aromatic substitution reactions, Friedel-Crafts alkylation of anisole, toluene or aromatic derivatives bearing an electron-releasing group is faster than benzene, giving primarily ortho- and para substituted products. The reaction is slowed by the presence of electron-withdrawing substituents (such as NO₂ in nitrobenzene and C=O in aryl ketones) on the aromatic ring. Indeed, Friedel-Crafts alkylation is very difficult with deactivated aromatic nuclei. The product distribution varies with the halide, the catalyst, the solvent and the aromatic substrate. As shown in Table 12.5,¹³² ortho-substituted products are generally preferred except with highly hindered alkyl halides such as *tert*-butyl. This preference for the ortho product has been called the **ortho effect** (additional stabilization of cation intermediates by an electron-releasing group to stabilize the intermediate generated by ortho-substitution relative to the intermediate generated by para substitution).¹³² Inspection of Table 12.5 shows that the ortho effect is more pronounced when the aromatic ring contains the stronger electron-releasing methoxy group (anisole) when compared to a methyl group (toluene). This effect is usually explained by the linear coordination of a heteroatom substituent with the incoming reagent.

^{129. (}a) Olah, G.A. Friedel-Crafts Chemistry, Wiley, New York, 1973, p 40; (b) Oláh, G.A.; Kuhn, S.; Oláh, J. J. Chem. Soc. 1957, 2174.

^{130.} Reference 129, p 41 (citation 471 in chapter II).

^{131.} Calloway, N.O. J. Am. Chem. Soc. 1937, 59, 1474.

^{132.} Olah, G.A.; Olah, J.A.; Ohyama, T. J. Am. Chem. Soc. 1984, 106, 5284.

In the case of oxygen substituents, an *O*-alkyl product can be formed, followed by an $O \rightarrow C$ migration, where migration to the ortho carbon is faster than migration to the para carbon.¹³³ Increasing the ability of the activating group to release electrons also correlates with a decrease in the yield of meta product. Separation of the isomeric arene products can be a problem.

When very active catalysts such as aluminum chloride are used for Friedel-Crafts alkylation with alkyl halides, significant amounts of meta products are often observed, even when the aromatic ring contains activating substituents.^{129a,b,130} Such products are due to the thermodynamic nature of the reaction with aluminum chloride, which shows a preference for the meta product. Excess catalyst and high reaction temperatures also favor more meta product. The use of BF₃, sulfuric acid, ferric chloride (FeCl₃) or zinc chloride (ZnCl₂) in lower concentrations and at lower temperatures, are preferred if primarily ortho-para products are the desired targets.¹³⁴

Friedel-Crafts alkylation with alkyl halides proceeds via a carbocation, and chiral alkyl halides are expected to give racemic arene products. The extent of racemization is dependent on the Lewis acid and the reaction conditions. As shown in Table 12.6,¹³⁵ Suga et al. found some asymmetric induction during the aromatic substitution, if the reaction temperature was maintained below 0°C and the reaction time was kept to a minimum. Reaction of (*S*)-2-chlorobutane and benzene gave **188** in up to 24% ee (*R*) using short contact times at low temperature. Some asymmetric induction was observed when mild Lewis acids were used, even at ambient temperatures. The use of strong Lewis acids, higher temperatures and longer contact times, however, led to the expected racemization. Presumably, at lower temperatures the C–Cl–M⁺X⁻ species is generated as a tight ion pair, where some asymmetric character is retained in the transition state of the reaction.

$\begin{array}{c} Cl & H \\ Me \end{array} \xrightarrow{ PhH } \begin{array}{c} Lewis acid \\ PhH \end{array} \xrightarrow{ PhH } \begin{array}{c} Me \\ Ph' \\ H \\ 188 \end{array}$							
Lewis Acid	<u>Temp. (°C)</u>	Time (min)	<u>% 188</u>	<u>% ee (R)</u>			
AlCl ₃	-30	0.8	100	24			
	-30	1.6	100	14			
	-30	2	100	12			
	-10	20	100	0			
FeCl ₃	0	40	70	24			
AlCl ₃ •MeNO ₂	30	15	30	13			
AlBr ₃	-30	1	100	0			

 Table 12.6
 Asymmetric Induction in the Friedel Crafts Reaction of (S)-2-Chlorobutane

^{133.} Kovacic, P.; Hiller Jr., J.H. J. Org. Chem. 1965, 30, 1581.

 ⁽a) Cullinane, N.M.; Leyshon, D.M. J. Chem. Soc. 1954, 2942; (b) Slanina, S.J.; Sowa, F.J.; Nieuwland, J.A. J. Am. Chem. Soc. 1935, 57, 1547.

^{135.} Suga, S.; Segi, M.; Kitano, K.; Masuda, S.; Nakajima, T. Bull. Chem. Soc. Jpn. 1981, 54, 3611.
The typical Friedel-Crafts alkylation disconnection is

12.4.B.ii. Isomerization, Polyalkylation and Deactivation. Several problems are associated with the Friedel-Crafts alkylation. The first occurs when primary and secondary halides are used, because the cations that are formed are subject to rearrangement. Reaction of benzene with 1-bromopropane and aluminum bromide (AlBr₃), for example, generated primary cation **189**. Rearrangement to the more stable secondary cation (**190**) was followed by reaction with benzene to give the final product, isopropylbenzene (cumene).¹³⁶ Due to this propensity for rearrangement, preparation of primary arenes (straight chain alkyl benzenes) is very difficult via Friedel-Crafts alkylation. On the other hand, the preparation of tertiary arenes (such as *tert*-butylbenzene), is straightforward because the easily formed tertiary cations usually do not rearrange.



Rearrangement can be accompanied by isomerization of the initially formed product due to the action of the Lewis acid (such as AlCl₃) required for the reaction.¹³⁷ Isomerization of groups can occur¹³⁸ via 1,2-shifts or via dissociation to a cation and readdition. 1,1-Dimethylpropylbenzene (191) dissociated in the presence of aluminum chloride to give 192, for example. Under these conditions, the reaction was reversible and addition of the cation to the aromatic ring generated two new carbocations, 193 (giving 194) or 195 (giving 196). The extent to which 196 is formed is related to the length of exposure of **191** to AlCl₃. This latter reaction is a thermodynamic process that favors the most stable isomer, and polyalkylation is also possible. Exposure of sec-butylbenzene (197) to the mixed-acid HF-BF₃ led to a mixture of 36.7% of benzene, 10.9% of *n*-butylbenzene, 21.8% of sec-butylbenzene and 30.6% of di-sec-butylbenzene.¹³⁹ Similarly, when *n*-butylbenzene was heated with aluminum chloride (100°C, 3 h), 45.2% of butylbenzene (99.4% *n*-butylbenzene and 0.6% sec-butyl-benzene), 15.2% of benzene, and 27.7% of dibutylbenzene (>90% meta) along with 11.9% of polyalkylated benzene products were obtained.¹⁴⁰ Lewis acid induced isomerization of dialkylbenzenes usually leads to an increase in the relative percentage of meta isomer, as seen with *n*-butylbenzene, based on the greater thermodynamic stability of the meta product than that of the ortho and para products.¹⁴¹

^{136.} Reference 129, p 68.

See (a) Nenitzesco, C.D.; Avram, M.; Sliam, E. Bull. Chim. Soc. Fr. 1955, 1266; (b) Nenitzescu, C.D.; Necsçoiu, I.; Glatz, A.; Zalman, M. Berichte 1959, 92, 10.

^{138.} Reference 129, p 70.

^{139.} McCaulay, D.A.; Lien, A.P. J. Am. Chem. Soc. 1953, 75, 2411.

^{140.} Kinney, R.E.; Hamilton, L.A. J. Am. Chem. Soc. 1954, 76, 786

^{141.} Taylor, W.J.; Wagmen, D.D.; Williams, M.G.; Pitzer, K.S.; Rossini, F.D. J. Res. Nat. Bur. Stand. 1946, 37, 95.



In Friedel-Crafts alkylation reactions, the alkyl substituents in the products are weakly electron releasing (and therefore activating), making the arene product more reactive than the benzene starting material. This increased reactivity leads to the second observed problem with Friedel-Crafts alkylation, **polyalkylation**. Alkylation of the arene leads to disubstituted products, which are often contaminants or occasionally, the major product in Friedel-Crafts alkylations. If benzene, for example, reacts with 2-chloropropane, the initial product is isopropylbenzene. Since isopropylbenzene is more reactive than benzene, it reacts with the carbocation intermediate in competition with benzene, leading to both o-diisopropylbenzene (198) and *p*-diisopropylbenzene (199) as secondary products. The steric hindrance inherent to formation of the ortho-disubstituted product can lead to a large proportion of the para product, if the steric interaction is severe. In a large excess of benzene, polyalkylation^{142,127b} can be suppressed. Francis¹⁴³ reported alkyl groups on benzene have only a small effect on the rate of Friedel-Crafts alkylation. Francis showed that "alkylation occurred in a heterogeneous reaction system, specifically in the catalyst layer and that the reason for polysubstitution is the preferential extraction of the early reaction product by this catalyst layer".¹⁴⁴ Using a solvent to solubilize both hydrocarbon and catalyst minimized polyalkylation, as does efficient (high speed) stirring and higher temperatures (which solubilizes the aluminum chloride).¹³⁸



 ⁽a) Price, C.C. Chem. Rev. 1941, 29, 37; (b) Thomas, C.A. Anhydrous AlCl₃ in Organic Chemistry, Reinhold, New York, 1941.

143. Francis, A.W. Chem. Rev. 1948, 43, 257.

^{144.} Reference 129, p 39.

When an aromatic ring contains several alkyl groups or complex alkyl groups, treatment with strong acids can lead to formation of isomeric polyalkyl benzene derivatives at relatively low temperatures (<100°C for methyl, room temperature for ethyl, and -80°C for isopropyl and *tert*-butyl).¹⁴¹ With weaker catalysts, higher temperatures are required. In an example involving simple groups, sulfonation of durene (**200**) led to **203**,¹⁴⁵ presumably via initial sulfonation to **201**, rearrangement to **202** and loss of sulfur trioxide (SO₃) to give **203**. This transformation has come to be known as the **Jacobsen rearrangement**.¹⁴⁶



Isomerization is minimized when an electron-withdrawing group is on the benzene ring



since the ring is deactivated, and less prone to further reaction. Acetophenone reacted with chloroethane (this reaction is sluggish and required using HF/SbF₅ as a catalyst) to give 3-ethylacetophenone (**204**) in 78% yield.¹⁴⁷

A third problem arises when a basic atom is present within the aromatic ring itself, as in pyrrole or pyridine, or is a substituent (as with aniline derivatives). Lewis acids react with the basic nitrogen to give the 'ate' complex (**205**, sec. 2.3), where the nitrogen takes a positive charge. This change in electron distribution deactivates the aromatic ring to substitution. The reaction also removes the catalyst from the reaction and the cation cannot be generated unless a large excess of Lewis acid is used. With aniline derivatives, the basic nitrogen atom can be protected (sec. 7.3). Conversion to an amide (such as *N*-acetylaniline from aniline, called acetanilide) withdraws electron density and diminishes the basicity of the amino group, allowing the Friedel Crafts reaction to give **206**.



^{145.} Hart, H.; Janssen, J.F. J. Org. Chem. 1970, 35, 3637.

147. Yoneda, N.; Fukuhara, T.; Takahashi, Y.; Suzuki, A. Chem. Lett. 1979, 1003.

 ^{146. (}a) Jacobsen, O. *Berichte* 1886, 19, 1209; (b) Smith, L.I. Org. React. 1942, 1, 370; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-48.

Friedel-Crafts isomerization disconnections are



Table 12.7. Selected Friedel-Crafts Catalysts and The Reactions They Catalyze

Catalyst	<u>Reactions</u> ^a	Catalyst	Reactions ^a	Catalyst	<u>Reactions^a</u>	
AlBr ₃	general	PBr ₃	al, deal	TiCl ₂ Et	al	
AlCl ₃	general	PCl ₃	al, deal	ZnEt ₂	al	
AlF ₃	poly, iso	PF ₃	al, deal	Al ₂ Br ₂ Et ₃	general	
AlI ₃	general	SiBr ₄	ac	HBF_4	al, poly	
AsF ₆	poly, al, ac, nitr	SiCl ₄	ac	HBr	poly	
BBr ₃	al, ac, poly	SiF ₄	ac, al, nitr	HCl	al, poly	
BCl ₃	al, ac, poly	SnCl ₂	ac, poly	HF	al, ac, poly	
BF ₃	general	SnCl ₄	ac, al, halo, poly	HI	ac	
BI ₃	al, ac	TiCl ₃	ac, al, poly	HClO ₄	ac, al, poly	
CaCl ₂	al	TiCl ₄	general	BF ₃ •OH ₂	al	
CaBr ₂	ac	ZnBr ₂	ac, al, halo	H_2SO_4	general	
CdCl ₂	poly	ZnCl ₂	general	H ₃ PO ₄	ac, al	
CeCl ₃	acetal formation	ZnI_2	al, ac, poly	PPA	ac, cycl, rearr	
CoCl ₂	for, al dehydr	$Al_2X_2R_n$	al	ClCH ₂ CO ₂ H	ac, poly	
CuBr ₂	halo, iso	AlEt ₂ Br	al	(ClCH ₂ CO) ₂ O	ac	
CuCl ₂	iso	AlEt ₃	al, poly	CCl ₃ CO ₂ H	chlor, poly	
FeBr ₃	al, ac, halo, poly, for	AlMe ₃	al	CF ₃ CO ₂ H	ac, chlor, iso	
FeCl ₃	general	$Al(t-Bu)_3$	al	$(CF_3CO)_2O$	ac, al, poly, cycl	
HgBr ₂	ac, halo, poly	Al(i-Bu)3	al, poly	RSO ₃ H	al, poly	
HgCl ₂	ac, al, iso, poly	Br ₃	al	PhSO ₃ H	al, poly	
MgBr ₂	al, ac, halo	MgR ₂	al, poly	TolSO ₃ H	al, poly	
MgCl ₂	al, iso	TiCl ₃ Me	al			
^a PPA = polyphosphoric acid ; al = alkylation; ac = acylation; chlor = chlorination; iso = isomerization; halo = halogenation; cycl = cyclization; poly = polymerization; for = formylation; dehydr = dehydration; nitr = nitration; general = active in most Friedel-Crafts reactions; deal = dealkylation; rearr = rearrangement.						
[Reprinted with permission from Olah, G.A. Friedel-Crafts Chemistry, Wiley, New York, 1973, pp. 298-304. Copyright © 1973 by John Wiley and Sons, Inc.]						

12.4.B.iii. Influence of the Catalyst. Lewis acids catalyze several different types of aromatic reactions, including alkylation, polymerization, isomerization, acylation (sec.12.4.D) and halogenation. Table 12.7.¹⁴⁸ shows the dependence of these reactions on various Lewis acids. This table shows a few common Lewis acids and the type of reaction(s) for which each is best suited. The relative strength of Lewis acids was discussed in Section 2.3. Olah gives a comprehensive list of Lewis acid catalysts, and includes several typical synthetic applications.¹⁴⁸ Metal alkyl catalysts are also effective catalysts, but the aromatic substrate is usually converted to a mono-, di-, or trialkyl derivative. Both metal halides and their alkyl derivatives are effective Friedel-Crafts catalysts as shown in Table 12.7,¹⁴⁹ as are common inorganic and organic acids.¹⁵⁰

^{148.} Reference 129, pp 298-304.

^{149.} Reference 129, p 327.

^{150.} Reference 129, p 342.

Triflate derivatives are actually trifluoromethanesulfonate esters ($-SO_2CF_3$, **OTf**), and they can be prepared with various metal counter ions. Triflates are effective catalysts in Friedel Crafts reactions. Some of the more common catalysts are B(OTf)₃, Al(OTf)₃, and Ga(OTf)₃.¹⁵¹

It is clear that many Lewis acids and protonic acids will catalyze various Friedel-Crafts reactions. The choice of halide, alkene, or alcohol substrate will determine which catalyst is used, although, as seen in Table 12.7, the type of reaction that is of interest is also dependent on the choice of catalyst. The following sections provide several examples to illustrate common catalysts used in various reactions, as well as the synthetic utility of the reaction.

12.4.C. Friedel-Crafts Reactions from Alkene and Alcohol Substrates

Friedel-Crafts alkylation occurs between an aromatic substrate and a carbocation. Carbocations can be generated from many precursors, including alkenes, alkynes or alcohols. Treatment of an alkene or an alkyne with a protonic acid catalyst generates a carbocation intermediate. A limiting feature of this process is the fact that a cationic intermediate formed in this manner can also react with the alkene or alkyne starting material, leading to cationic polymerization as a competitive side reaction. The usual problems of polyalkylation and rearrangement associated with aromatic substitution persist. For example, toluene reacts with propene to give isopropylbenzene in 52%,¹⁵² 20% of diisopropyl-benzene, 3% of trisubstituted products and 1.3% of tetrasubstituted products were formed when 0.75 equivalents of propene were used. As shown in Table 12.8,¹⁵² toluene and ethene react to give a wide array of products. The nature of those products is completely dependent on the relative amount of ethene.

$Me \frac{CH_2=CH_2}{Lewis acid}$							
Equivalents of Ethene	<u>PhH</u>	<u>PhEt</u>	<u>di-Et</u>	<u>tri-Et</u>	<u>tetra-Et</u>	<u>penta-Et</u>	<u>hexa-Et</u>
0.20	87.9	10.9	1.24				
0.50	80.8	15.5	2.14	0.67	0.15	0.06	0.67
0.56	80.5	15.2	1.67	0.71			1.91
1.14	31.6	35.2	21.1	4	2.4	2.8	2.82
1.68	35.4	23.4	13.6	6.3	4.2	3.6	13.4
3.66	0.2	1.1	10.6	56.2	11.6	1.5	18.7
5.24				7.00	18.8	2.4	7.8
5.74					8.5	0.9	90.6
[Reprinted with permission from OBerry, T.M.; Reid, E.E. J. Am. Chem. Soc. 1927, 49, 3142. Copyright © 1927 American Chemical Society.]							

 Table 12.8. Polyalkylation Products from the Reaction of Toluene and Ethene

Hydrogen fluoride (HF) is often used as a catalyst for alkenes since there is less decomposition and fewer polymeric by-products. In addition, the volatile catalyst is easily removed.¹⁵³ Both

^{151.} Olah, G.A.; Farooq, O.; Farnia, S.M.F.; Olah, J.A. J. Am. Chem. Soc. 1988, 110, 2560.

^{152.} Berry, T.M.; Reid, E.E. J. Am. Chem. Soc. 1927, 49, 3142.

^{153.} Reference 129, p 44.

ferric chloride (FeCl₃) and BF₃ are common catalysts for coupling alkenes with aromatic rings. Typical alkyne catalysts¹⁵⁴ are aluminum chloride, gallium trichloride (GaCl₃), BF₃ or sulfuric acid. Reaction of a mixture of xylenes with a trace amount of BF₃ in liquid HF gave the thermodynamic mixture of 18% ortho, 60% meta and 22% para, but treatment with excess BF₃ gave virtually 100% *m*-xylene.^{143,142b,155}

Friedel-Crafts alkylations using alkene substrates are most useful when stable cations are formed and when done intramolecularly, as observed with alkyl halide precursors. Internal Friedel-Crafts cyclization using alkene substrates forms the basis of many natural product syntheses. Majetich and Zhang treated **207** with TiCl₄ in a synthesis of perovskone,¹⁵⁶ and obtained a 95% yield of **208**. In this case, a primary cation led to the final product, due to stabilization by extended conjugation with the carbonyl unit. In the Sames and co-worker's synthesis of the core of teleocidin B4,¹⁵⁷ **209** was treated with methanesulfonic acid in dichloromethane. The alkene unit was converted to a carbocation that reacted with the proximal benzene ring by an intramolecular Friedel-Crafts alkylation to give an 83% yield of **210**.



Alcohols are common precursors to carbocations, and they are often used as substrates in Friedel-Crafts alkylation reactions. Sulfuric acid is used as a catalyst with alcohols, forming an alkyl sulfate that reacts with the aromatic substrate.¹⁵⁸ Alcohols are more reactive than halides, although large quantities of a Lewis acid are usually required for Friedel-Crafts reactions.¹⁵⁹ Alcohols form a complex with aluminum chlorides [R(H)O \rightarrow AlCl₃], and a complicating side reaction is loss of HCl from the complex, with formation of an alkyl chloride.¹⁶⁰ A full equivalent

- 158. (a) Günther, F. U.S. Patent 1,670,505, 1928 [Chem. Abstr., 22: 2378, 1928]; (b) Reference 129, p 47.
- 159. Norris, J.F.; Sturgis, B.M. J. Am. Chem. Soc. 1939, 61, 1413.

^{154.} Reference 129, ,p. 45.

^{155.} McCaulay, D.A.; Shoemaker, B.H.; Lien, A.P. Ind. Eng. Chem. 1950, 42, 2103.

^{156.} Majetich, G.; Zhang, Y. J. Am. Chem. Soc. 1994, 116, 4979.

^{157.} Dangel, B.D.; Godula, K.; Youn, S.W.; Sezen, B.; Sames, D. J. Am. Chem. Soc. 2002, 124, 11856.

^{160.} Reference 129, p 46.

of the Lewis acid is required to form the complex. In a synthesis of (–)-aphanorphine, Zhai and co-workers¹⁶¹ treated alcohol **211** with aluminum chloride and obtained an 88% yield

$$MeO \underbrace{211}^{H} OH \underbrace{AlCl_3, CH_2Cl_2}_{OH} MeO \underbrace{212}_{He} MeO \underbrace{1212}_{He} MeO \underbrace{1212}_{$$

of **212**. This is an interesting example because it generated an azabicyclo[3.2.1] system from a tertiary alcohol with good selectivity for the diastereomer

shown. Other oxygen-stabilized carbocations add to aromatic rings, including heteroaromatic rings. In Movassaghi and Ondrus' synthesis of tricyclic *Myrmicarin* alkaloids,¹⁶² treatment of the acetal unit in **213** with aqueous acetic acid generated the carbocation and cyclization led to a quantitative yield of **214** with >10:1 regioselectivity after elimination of the initially formed hydroxy compound. Other cation precursors can be used in these reactions. Locher and Peerzada used a benzotriazole unit in a synthesis of tetrahydroisoquinolines.¹⁶³ In this reaction, **215** was converted to **216** in 87% yield under very mild conditions.



Typical Friedel-Crafts disconnections involving alcohol and alkene precursors are



12.4.D. Friedel-Crafts Acylation

The reaction of a Lewis acid reacts and an acyl halide or an anhydride produces a resonance stabilized acylium ion (217). The π bond of a benzene ring attacks carbocation 217 to produce the usual Wheland intermediate 218, and loss of a proton accompanied by aromatization gives

^{161.} Zhai, H.; Luo, S.; Ye, C.; Ma, Y. J. Org. Chem. 2003, 68, 8268.

^{162.} Movassaghi, M.; Ondrus, A.E. Org. Lett. 2005, 7, 4423.

^{163.} Locher, C.; Peerzada, N. J. Chem. Soc. Perkin Trans. 1 1999, 179.

an aryl ketone (**219**). This reaction is known as **Friedel-Crafts acylation**.^{164,127a} The carbonyl group in the ketone product is polarized δ + and attached directly to the aromatic ring, so it is deactivated relative to benzene. Since **219** is less reactive than benzene, further reaction to give a polyacylated derivative is not a major problem. In other words, Friedel-Crafts acylation does not lead to polyacylation. The resonance stabilized acylium ion (**217**) is not subject to skeletal rearrangement prior to reaction with the aromatic ring. Isomerization of the ketone product is not a problem.



Acylium ions can be produced from acyl bromides and iodides, but the more common and more stable acid chlorides are typically used. Table 12.9¹⁶⁵ shows the efficacy of several catalysts for the reaction of benzoyl chloride and anisole. In all cases, the para product (**221**) predominated over the ortho product (**220**) by about 31:1.¹⁶⁵ Mild Lewis acids can be used to effect Friedel-Crafts cyclization, which is particularly important with synthetic targets bearing other functional groups. The acylation is not limited to benzene, of course, but deactivated aromatic rings either do not undergo Friedel-Crafts reactions at all, or do so with difficulty. Activated aromatic rings react in most cases. In a synthesis of calothrixin A by Chai and Bernardo,¹⁶⁶ acid chloride **222** reacted with indole in the presence of MeMgCl/ZnCl₂ to give a 90% yield of **223**.

Table 12.9.	ortho/para	Selectivity as	a Function of	Lewis Acid i	n Friedel-	Crafts Acylation

MeO \swarrow $\xrightarrow{Ph}^{O}_{Cl}$ \xrightarrow{OMeO}_{Ph} \xrightarrow{Ph}_{Ph} \xrightarrow{Ph}_{O} \xrightarrow{Ph}_{O}					
<u>Catalyst</u>	<u>% 220 + 221</u>	<u>Catalyst</u>	<u>% 220 + 221</u>	<u>Catalyst</u>	<u>% 220 + 221</u>
ZnCl ₂	93	SnCl ₄	90	MoCl ₅	80
FeCl ₃	83	SbCl ₅	43	NbCl ₅	54
AlCl ₃	52	TaCl ₅	52	BiCl ₃	49
TUC		-	• •		25
WCl ₆	47	ZrCl ₄	39	T ₁ Cl ₄	35

^{164.} For reactions of this type of reaction, see reference 79, pp 1422-1433. Also see (a) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-34; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 254-255.

^{165. (}a) Tsukervanik, I.P.; Veber, N.V. Dokl. Akad. Nauk. SSSR 1968, 180, 892; (b) Reference 129, p 195.

^{166.} Bernardo, P.H.; Chai, C.L.L. J. Org. Chem. 2003, 68, 8906.



Other carboxylic acid derivatives can be used in Friedel-Crafts acylation reactions, including anhydrides and esters. Chai and co-workers prepared **224** in 85% yield using dibutyl anhydride with perchloric acid, in a synthesis of hybocarpone.¹⁶⁷ Lactones are also effective substrates in this cyclization, generating ketones.¹⁶⁸



Intramolecular Friedel-Crafts acylations are extremely valuable for the synthesis of polycyclic compounds. The length of the tether directly influences the site of attack on the aromatic nucleus and the facility of the cyclization. The aromatic nucleus can be benzene, another simple aromatic compound, a polynuclear aromatic hydrocarbon or a heteroaromatic compound

such as pyrrole, furan or thiophene. The importance to tether length can be illustrated by the reaction of pyrrole-diester **225** with BBr₃, which led to ketone **226** in Vallée and coworker's synthesis of (R)-(+)myrmicarin 217.¹⁶⁹ In intermolecular Friedel-Crafts



acylation reactions, pyrroles usually give the α -acyl derivative with the soft acylium electrophile (sec. 2.4). Using hard electrophiles such as trimethylsilyl triflate (Me₃SiOTf), however, led to the β -derivative.¹⁷⁰ When pyrrole was treated with acetic anhydride (at 150-200°C), a mixture of 2-acetylpyrrole and 2,5-diacetylpyrrole was formed by reaction with the soft acylium ion.¹⁷¹ Acylation of an *N*-silyl pyrrole led predominantly to the β isomer rather than the α isomer (an 83:17 mixture in 46% yield), when reacted with either anhydrides or acyl chlorides.¹⁷² The bulky -SiMe₃ group presumably blocked the C2 position. A somewhat more traditional example taken from Baati, Misokowski and co-worker's synthesis of rhein and diacerhein,¹⁷³ treated acid **227** with trifluoroacetic acid to give ketone **228** in 96% yield.

- 167. Chai, C.L.L.; Elix, J.A.; Moore, F.K.E. J. Org. Chem 2006, 71, 992.
- 168. Inouye, Y.; Uchida, Y.; Kakisawa, H. Chem. Lett. 1975, 1317.
- 169. Sayah, B.; Pelloux-Léon, N.; Vallée, Y. J. Org. Chem. 2000, 65, 2824.
- 170. Simchen, G.; Majchrzak, M.W. Tetrahedron Lett. 1985, 26, 5035.
- 171. Katritzky, A.R. Handbook of Heterocyclic Chemistry, Pergamon Press, Oxford, 1985, p 254.
- 172. McCombie, S.W.; Shankar, B.B.; Ganguly, A.K. Tetrahedron Lett. 1987, 28, 4123.
- 173. Gonnot, V.; Tisserand, S.; Nicolas, M.; Baati, R.; Mioskowski, C. Tetrahedron Lett. 2007, 48, 7117.



For benzene derivatives, both ortho positions are subject to acylation if they do not bear substituents. As shown in Table 12.10,¹⁷⁴ Friedel-Crafts acylation of **229** gave a mixture of coumarins **230** and **231**. Sulfuric acid gave a mixture favoring **231**, whereas a mixture of phosphorus pentabromide and aluminum chloride (PBr₅/AlCl₃) was highly regioselective for the formation of **230**. It is clear that the ortho selectivity depends upon the catalyst used, as well as upon the nature of the substrate. A related acylation procedure uses iminium salts rather than acyl halides. The **Vilsmeier-Haack** reaction¹⁷⁵ is a well-known process, illustrated by reaction of pyrrole with the POCl₃ complex of *N*,*N*-dimethylacetamide (**232**, which can decompose to a chloroiminium salt). The acylation reaction initially gave **233**, which was converted to 2-acetylpyrrole by hydrolysis with aqueous sodium acetate.¹⁷⁶ A synthetic example is taken from a synthesis of lactonamycin by Barrett and co-workers,¹⁷⁷ in which **234** reacted with POCl₃ and DMF and then aqueous sodium acetate to give aldehyde **235** in 75% yield.

$\begin{array}{c} Cl \\ Cl \\ Cl \\ 229 \end{array} \xrightarrow{CO_2H} \xrightarrow{CO_2H} $	$- \begin{array}{c} Cl \\ Cl \\ Cl \\ 230 \end{array} + \begin{array}{c} Me \end{array}$	$\begin{array}{c} CI & O \\ CI & & \\$
<u>Reagent</u>	<u>% Yield</u>	<u>230 : 231</u>
H_2SO_4	65	35:65
MeSO ₃ H/P ₂ O ₅	70	50:50
PCl ₅ /AlCl ₃	90	85:15
PBr ₃ /AlCl ₃	87	95 : 5
[Reprinted with permission from	n Dr. Frank Urban, Pfizer Cent	ral Research, Groton, CT.]

Table 12.10. Regioselectivity in a Friedel-Crafts Synthesis of Coumarins

^{174.} Provided through the courtesy of Dr. Frank Urban, Pfizer Central Research, Groton, CT, from (a) Lipinski, C.A. U.S. Patent 4,853,410, 1989; EP 230379A2, 1988 [Chem. Abstr. 108 : 75224h, 1988]; (b) Moore, B.S. Unpublished results.

⁽a) Vilsmeier, A.; Haack, A. *Berichte* 1927, 60, 119; (b) deMaheas, M.R. *Bull. Chim. Soc. Fr.* 1962, 1989;
(c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-96; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 558-559.

^{176.} Reference 171, p 254.

^{177.} Wehlan, H.; Jezek, E.; Lebrasseur, N.; Pave, G.; Roulland, E.; White, A. J.P.; Burrows, J.N.; Barrett, A.G.M.. Org. Chem. 2006, 71, 8151.



A variation of the Vilsmeier-Haack reaction uses a formamide such as **236** with benzene (or another aromatic compound) to give the aromatic aldehyde and the amine precursor to the formamide (*N*-methylaniline in this case).^{175a} A solvent-free Vilsmeier reaction has been reported using microwave irradiation on silica gel.¹⁷⁸



12.4.E. Synthesis of Polycyclic Aromatics That Do Not Contain Nitrogen

A classical reaction that exploits the power inherent to Friedel-Crafts techniques is the **Haworth phenanthrene synthesis**,¹⁷⁹ which uses anhydrides in a Friedel-Crafts reaction with aromatic compounds, to prepare polynuclear aromatic derivatives in a stepwise manner. When 1-methylnaphthalene (237) was heated with succinic anhydride in the presence of AlCl₃, keto acid 238 was formed. Clemmensen reduction (sec. 4.9.G) of the ketone gave 239, and a second Friedel-Crafts cyclization in the presence of sulfuric acid led to the tricyclic ketone, 240. Reduction of the carbonyl and aromatization (by heating with selenium led to phenanthrene 241. Direct cyclization of the acid occurred when a more vigorous catalyst (sulfuric acid) was used, and there was no need to form the acid chloride first. If benzene were used as a starting material in this sequence, a naphthalene derivative would be formed. Intermediate products such as 240 are important for other synthetic work, making this sequence even more useful. In a synthesis of hamigeran B by Clive and Wang,¹⁸⁰ *m*-cresol was converted to 242 by the modified Haworth synthesis shown. Note the use of Zn/HCl/HgCl₂ for reduction of the ketone

^{178.} Paul, S.; Gupta, M.; Gupta, R. Synlett 2000, 1115.

^{179. (}a) Haworth, R.D. J. Chem. Soc. 1932, 1125; (b) Haworth, R.D.; Mavin, C.R. Ibid. 1932, 2720; (c) Haworth, R.D. Ibid. 1932, 2717; (d) Haworth, R.D.; Letsky, B.M.; Mavin, C.R., Ibid. 1932, 1784; (e) Haworth, R.D.; Bolam, F.M. Ibid. 1932, 2248; (f) Haworth, R.D.; Mavin, C.R.; Sheldrick, G., Ibid. 1934, 454; (g) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-41.

^{180.} Clive, D.L.J.; Wang, J. J. Org. Chem. 2004, 69, 2773.

after acylation with succinic anhydride, and POCl₃ to initiate the Friedel-Crafts acylation with the carboxylic acid.



Another useful sequence that produces polynuclear aromatic compounds is the **Bally-Scholl synthesis**.¹⁸¹ This variation involves addition of a glycerol derivative (a 1,2,3-propanetriol) to an aromatic ring. An example is the reaction of anthraquinone (**243**) with 1,2,3-pentanetriol (**244**, also called α -ethylglycerol) to form an alkenyl diol, **245**. Elimination to diene **246** was followed by ring closure under the acidic conditions to give **247** (1-ethylmesobenzanthrone) in about 5% yield.¹⁸² Poor yields with such multistep processes are common under the strongly acidic conditions used. In many other types of reactions, milder conditions involving milder Lewis acids and structural changes in the substrate led to enhanced yields. Poor yields such as that observed for **247** may be acceptable if the synthesis is relatively straightforward, and there are few alternative synthetic routes.



Another Friedel-Crafts route to phenanthrenes is the **Bardhan-Sengupta phenanthrene** synthesis.¹⁸³ When phenethylcyclohexanol 248 was cyclized with phosphorus pentoxide at 140°C, the product was 249.¹⁸³ Aromatization was accomplished by heating with selenium to give phenanthrene derivative 250 (1-methyl-7-isopropylphenanthrene, otherwise known as retene).¹⁸³ An improvement in the reaction used hydrogen fluoride (HF) to induce cyclization.¹⁸⁴

184. Renfrow, W.B.; Renfrow, A.; Shoun, E.; Sears, C.A. J. Am. Chem. Soc. 1951, 73, 317.

 ⁽a) Bally, O. Berichte 1905, 38, 194; (b) Bally, O.; Scholl, R. Ibid. 1917, 44, 1656; (c) Meerwein, H.; Klinz, J. J. Prakt. Chem. 1918, 97, 235.

^{182.} Baddar, F.G.; Warren, F.L. J. Chem. Soc. 1938, 401.

^{183.} Bardhan, J.C.; Sengupta, S.C. J. Chem. Soc. 1932, 2520, 2798.



Both phenanthrenes and hydronapthalenes are available by the **Bogert-Cook synthesis**.^{185,183} When the Grignard reagent derived from **251** reacted with 2,5-dimethylcyclohexanone, alcohol **252** was produced in 43% yield. Treatment with 85% sulfuric acid effected dehydration of the alcohol to a cyclohexene derivative, which closed on the aromatic ring to give **253** in 81% yield. Dehydrogenation with selenium at 300°C gave retene (**250**), whereas hydrogenation with Raney nickel (sec. 4.8.F) gave abietane (**254**) in 39% yield.¹⁸⁶ The use of 1-bromonaphthalene derivatives as a starting material will lead to larger polycyclic rings.^{185b} An alkene unit can also be used to generate a cation and subsequent cyclization will generate a polycyclic aromatic compound. The reaction of **255** with acetaldehyde gave **256**, which was cyclized by treatment with sulfuric acid to give hydronapthalene (**257**). This modification does not incorporate the additional ring of the cyclic ketones used in the Bogert-Cook reaction; it is sometimes called the **Bogert synthesis**.



tetralin synthesis.¹⁸⁷ In this process, the alkenyl group is used directly as the cation precursor. An example is treatment of **258** with

- 185. (a) Bogert, M.T. Science 1933, 77, 289; (b) Cook, J.W.; Hewett, C.L. J. Chem. Soc. 1933, 1098.
- 186. Sterling, E.D.; Bogert, M.T. J. Org. Chem. 1939, 4, 20.

259

Me

<45°C

258

187. (a) Darzens, G. Compt. Rend. 1926, 183, 748; (b) Idem, Ibid. 1935, 201, 730; (c) Darzens, G.; Lévy, A. Ibid. 1936, 202, 427; (d) Idem, Ibid. 1936, 203, 669; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-22.

concentrated sulfuric acid, followed by gentle heating to give the tetralin (tetrahydronaphthalene, **259**).¹⁸⁸ The difference between this and the Bogert synthesis is the method used to form the alkenyl arene. Tetralin formation from an alkenylbenzene derivative is most often referred to as the Darzens tetralin synthesis rather than the Bogert synthesis.



The **Bradsher reaction**¹⁸⁹ is a synthetic route that converts aryl ketones (260) to polycyclic hydrocarbons such as 261. This reaction can also be applied to heterocyclic derivatives of 260 (X = O, S, Se). A common route to ketones such as 260 is

shown for the preparation of **266**. Two aryl groups were incorporated by a Grignard reaction of aldehyde **262** with phenylmagnesium bromide, producing **263** in 81% yield. Subsequent treatment with cuprous cyanide (also see sec. 2.11.E) led to nitrile **264**, and reaction with ethylmagnesium bromide gave the ketone (**265**). Subsequent reaction with HBr (reflux for four days) generated ethyl anthracene (**266**) in 69% yield.^{189a}



(a) i. PhMgBr ii. I₂, P, AcOH, reflux, 29 h (b) CuCN, 250°C, 23 h (c) i. EtMgBr, PhH, reflux, 20 h ii. H₃O⁺ (d) 30% HBr, AcOH, 4 d

Note that the alkene reactions given in this section suggest that Friedel-Crafts cyclizations are sensitive to minor changes in substrate and reaction conditions.

The disconnections found in this section are



12.5. FRIEDEL-CRAFTS REACTIONS: FORMATION OF HETEROATOM-CONTAINING DERIVATIVES

Friedel-Crafts alkylation and acylation reactions are quite versatile. They form the basis of several named reactions that have been used to synthesize heteroatom-containing compounds such as quinolines, isoquinolines, and many others. This section examines several of the more common transformations that will show the scope and utility of these processes. It will also introduce a modest amount of heterocyclic chemistry into our synthetic discussion.

^{188.} Darzens, G.; Lévy, A. Compt. Rend. 1935, 200, 469.

^{189. (}a) Bradsher, C.K. J. Am. Chem. Soc. 1970, 62, 486; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-14.

12.5.A. Synthesis of Quinoline Derivatives

The quinoline unit is an essential feature of many natural products, and there are several reactions that generate quinolines. One of the older, yet still useful methods, is the **Knorr quinoline synthesis**.¹⁹⁰ This reaction couples an aromatic amine (usually aniline or a derivative) with a β -keto ester. This particular reaction is subject to formation of regioisomeric products, depending on the temperature and reaction conditions. Heating aniline and ethyl acetoacetate to 140°C, for example, gave 50% of **268**. However, if aniline and ethyl acetoacetate were reacted at room temperature for 5 days (or for 3 days with a catalytic amount of HCl), 60% of the isomeric hydroxyquinoline **267** was isolated. A 70% yield of **267** was also obtained when aniline was treated with ethyl acetoacetate in ethanol with a catalytic amount of acetic acid in the presence of Drierite[®] In an example taken from a synthesis of diplamine, by Heathcock and Szczepankiewicz,¹⁹¹ initial coupling of aniline derivative **269** with β -keto ester **270** gave keto amide **271** in 83% yield. Subsequent treatment with 90% sulfuric acid at 75°C led to the Knorr quinoline reaction that gave **272** in 82% yield. Further modification was required for the synthesis, and heating this pyridone derivative with POCl₃ gave a 94% yield of the 2-chloroquinoline derivative **273**.



^{190. (}a) Knorr, L. Annalen 1886, 236, 69; (b) Idem, Ibid. 1888, 245, 357; (c) Bergström, F.W. Chem. Rev. 1944, 35, 77 (see p 157). Also see (c) Hodgkinson, A.J.; Staskun, B. J. Org. Chem. 1969, 34, 1709; (d) Hauser, C.R.; Reynolds, G.A. J. Am. Chem. Soc. 1948, 70, 2402; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-52;.

^{191.} Szczepankiewicz, B.G.; Heathcock, C.H. J. Org. Chem. 1994, 59, 3512.

The lower temperature variation of this reaction initially forms an imine or an enamine. Friedel Crafts cyclization gave the 4-hydroxyquinoline in what is called the **Conrad-Limpach reaction**.¹⁹² This reaction generally gives the opposite regioisomeric product to that obtained by the Knorr quinoline synthesis. The initially formed product is usually the enamine (as in the formation of **274** from aniline and ethyl acetoacetate).¹⁹³ Under acidic conditions the iminium salt was formed and cyclized with the aromatic ring. A more efficient method simply heated **274** to 250°C in mineral oil, giving a 90% yield of **275**. A variety of other functional groups can be tolerated in the molecule when this procedure is used.



The Knorr and Conrad-Limpach disconnections are



The **Gould-Jacobs reaction**¹⁹⁴ is related to the reactions just described, in that an aromatic amine such as **276** is reacted with EtOCH=C(CO₂Et)₂ to generate an enamino ester (**277**). Heating to 250°C induced cyclization to give 4-hydroxyquinoline ester **278** in 83% yield.^{194a} Saponification gave 4-hydroxy-5,6-benzoquinidine-3,7-dicarboxylic acid, **279**.¹⁹⁵ This sequence can be used with many aromatic substrates, but when secondary amines are used as precursors the reaction takes a slightly different course. 2-Methoxy-*N*-ethylaniline (**280**) was converted to **281** (80% yield) in the same manner. Subsequent cyclization^{194a} in the presence of P₂O₅ required only 140°C to give an 85% yield of **282**. The presence of a tertiary amine moiety in this product prevented aromatization, and decarboxylation led to **283** in 41% yield.

^{192. (}a) Conrad, M.; Limpach, L. Berichte 1887, 20, 944; (b) Idem Ibid. 1891, 24, 2990; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-19; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 166-167.

^{193. (}a) Manske, R.H. Chem. Rev. 1942, 30, 113 (see p 121); (b) Reitsema, R.H. Ibid. 1948, 43, 43 (see p 47).

^{194. (}a) Gould Jr., R.G.; Jacobs, W.A. J. Am. Chem. Soc. 1939, 61, 2890; (b) Reference 193b, see p 53; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-37; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 278-279.

^{195. (}a) Markees, D.G.; Schwab, L.S. *Helv. Chim. Acta* 1972, 55, 1319; (b) Albrecht, R.; Hoyer, G.-A. *Berichte* 1972, 105, 3118.



The Gould-Jacobs disconnection is



If a β -diketone is used rather than a β -keto ester, the result is a 4-alkylquinoline in what is known as the **Combes quinoline synthesis**.¹⁹⁶ Reaction of aniline with acetyl acetonate (2,5-pentanedione), for example, generated enamine **284** (the tautomer of imine **285**). Enolization to **286** in the presence of HF was followed by cyclization to give quinoline **287** in 96% yield.^{197,156a}



^{196. (}a) Combes, A. Bull. Chim. Soc. Fr. 1888, 49, 89; (b) Reference 190c, see p 156; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-19; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 164-165.

197. Born, J.L. J. Org. Chem. 1972, 37, 3952.

The **Doebner-Miller reaction**¹⁹⁸ is the reaction of a primary aromatic amine (such as aniline) with a carbonyl compound such as acetaldehyde in the presence of acid to give a 2-alkylquinoline. Reaction of aniline with acetaldehyde gave **288**, but a subsequent aldol condensation with the imine derived from acetaldehyde (sec. 9.4.F.i) led to **289**.¹⁹⁹ Friedel-Crafts cyclization was followed by loss of aniline to give **290**, and aromatization gave 2-methylquinoline (**291**).



The Combes and Doebner-Miller disconnection is

The **Doebner reaction**^{200,196b} condensed aromatic amines and aldehydes with pyruvic acid derivatives. Reaction of *p*-toluidine with pyruvic acid (**292**) gave the γ -aminopyruvic acid (**293**) *in situ*, and subsequent cyclization and air oxidation under Friedel-Crafts conditions generated the 4-carboalkoxyquinoline (**294**).²⁰¹ Presumably, the reaction proceeds via initial imine formation (via reaction with benzaldehyde) followed by condensation with pyruvate in its enol form.^{190cd} Similar cyclization occurs with imines and pyruvate derivatives.²⁰²



The Doebner disconnection is



198. (a) Doebner, O.; Miller, W. Berichte 1883, 16, 2464; (b) Reference 190c, see p 154.

- 201. Döbner, O.; Gieseke, M. Annalen 1887, 242, 290.
- 202. Cuisa, R.; Musajo, L. Gazz. Chim. Ital 1929, 59, 796.

^{199. (}a) Ogata, Y.; Kawasaki, A.; Suyama, S. J. Chem. Soc. B 1969, 805; (b) Forrest, T.P.; Dauphinee, G.A.; Miles, W.F. Can. J. Chem. 1969, 47, 2121.

^{200. (}a) Döbner, O. Annalen 1887, 242, 265; (b) Idem, Berichte 1887, 20, 277; (c) Idem Ibid. 1894, 27, 352, 2020; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-25; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 212-213.

The **Skraup reaction**²⁰³ presents another variation in which an aniline derivative reacts with glycerol in the presence of acid, to generate a quinoline derivative. Rapoport reacted 3-aminopyridine (**295**) with glycerol to produce **296** (1,5-naphthyridine) in 31% yield.²⁰⁴ It is important to note that none of the isomeric 1,7-naphthyridine (**297**) was produced in this reaction. Attack at the carbon adjacent to both nitrogens seems to be the preferred regioselectivity with aminopyridines. The reaction is regioselective²⁰⁵ rather than regiospecific, however, since Rapoport reported about 4% of 3-methyl-1,5-naphthyridine and 3-ethyl-1,5-naphthyridine. This is obviously related to the **Bally-Scholl synthesis** introduced in sec. 12.4.E.



The Skraup disconnection is:



12.5.B. Synthesis of Isoquinoline Derivatives

Isoquinolines are as important as quinolines in the chemistry of natural products, and there are also many syntheses of these compounds. One of the most important Friedel-Crafts routes is the **Bischler-Napieralski reaction**.²⁰⁶ This process is the reaction of an *N*-acyl amine such as **298** derived from phenethylamine, with a reagent such as PPA or P_2O_5 to give a dehydroisoquinoline derivative (**299**). For example, in a synthesis of stepharine²⁰⁷ Honda and Shigehisa treated acetamide **300** with POCl₃, and obtained **301**, which gave **302** in >60% overall yield after treatment with trifluoroacetic acid and triethylamine.

^{203. (}a) Skraup, Z.H. Berichte 1880, 13, 2086; (b) Manske, R.H.; Kulka, M. Org. React. 1953, 7, 59; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-87; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 602-603.

^{204.} Rapoport, H.; Batcho, A.D. J. Org. Chem. 1963, 28, 1753.

^{205. (}a) Perche, J.-C.; Saint-Ruf, G.; Buu-Hoï, N.P. J. Chem. Soc. Perkin Trans. 1 1972, 260; (b) Buu-Hoï, N.P.; Jacquignon, P.; Thang, D.C.; Bartnik, T. Ibid. 1972, 263.

^{206. (}a) Bischler, A.; Napieralski, B. Berichte 1893, 26, 1903; (b) Bischler, A. Ibid. 1893, 26, 189, 1891; (c) Whaley, W.M.; Govindachari, T.R. Org. React. 1951, 6, 74; (d) Fodor, G.; Gal, J.; Phillips, B.A. Angew. Chem. Int. Ed. 1972, 11, 919; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-11; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 96-97.

^{207.} Honda, T.; Shigehisa, H. Org. Lett. 2006, 8, 657.



A useful variation first converts the amino group to a formamide derivative, usually by treatment of a ketone (such as **303**) with formamide and formic acid. Treatment of **303** with these reagents led to formamide **304**. When treated with POCl₃, cyclization occurred via the *N*-acyl group to give the isoquinoline, **305**, in 66% yield. Zee-Cheng and Cheng used this sequence in a synthesis of nitidine.²⁰⁸



Bischler-Napieralski disconnections are

The **Pictet-Spengler isoquinoline synthesis** is another classical approach.^{209,206c} This variation generates an iminium salt from an amine and an aldehyde (a Schiff base), which cyclizes with an aromatic ring to complete the reaction.²¹⁰ A synthetic example is taken from a synthesis of (–)-fuchsiaefoline by Cook and co-workers.²¹¹ The reaction of amino ester **306** with the indicated aldehyde gave a near quantitative yield of **307**, but as a mixture of cis/trans isomers rather than the single epimer shown. Treatment of this mixture with about five equivalents of

^{208.} ZeeCheng, K.Y.; Cheng, C.C. J. Heterocyclic Chem. 1973, 10, 85.

⁽a) Pictet, A.; Spengler, T. *Berichte, 1911, 44*, 2030; (b) Cox, E.D.; Cook, J.M. *Chem. Rev. 1995, 95*, 1797;
(c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-73; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 508-509.

^{210.} Ong, H.H.; May, E.L. J. Heterocyclic Chem. 1971, 8, 1007.

^{211.} Zhou, H.; Liao, X.; Cook, J.M. Org. Lett. 2004, 6, 249.

trifluoroacetic acid in dichloromethane and stirring for seven days gave a 92% yield of 307.



Modifying groups on the aromatic ring can control the regioselectivity of the reaction. A typical Pictet-Spengler reaction with formaldehyde converted **308** to **309** in 22% yield. The silyl directed reaction, however, converted **310** to **311** in 72% yield.²¹² Jacobsen and Taylor reported a Pictet-Spengler reaction, catalyzed by a chiral thiourea derivative that gave the product in good yield, with excellent enantioselectivity.²¹³ A microwave-accelerated Pictet-Spengler reaction has also been used to prepare indole alkaloids.²¹⁴



The Pictet-Spengler disconnection is

$$\begin{array}{|c|c|c|c|c|}
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Another method for the synthesis of isoquinoline derivatives is the **Pomeranz-Fritsch** reaction.²¹⁵ Simple aniline derivatives can be used, but the reaction is most useful for acid sensitive substrates such as thiophene or pyrrole derivatives. In those cases, it is a good alternative to the Pictet-Spengler reaction. An example of an acid sensitive substrate is **312**, which reacted with glycinal diethyl acetal (**313**) to generate Schiff base **314** in 91% yield. Subsequent treatment with PPA/POCl₃ gave a 21% yield of pyrrolo-[1,2*a*]-pyrazine (**315**).²¹⁶ When the reactive partners were reversed to α -methylbenzylamine (**316**) and a glyoxal semiacetal (**317**), a different Schiff base was formed (**318**). Treatment with acid led directly to

^{212.} Miller, R.B.; Tsang, T. Tetrahedron Lett. 1988, 29, 6715.

^{213.} Taylor, M.S.; Jacobsen, E.N. J. Am. Chem. Soc. 2004, 126, 10558.

^{214.} Kuo, F.-M.; Tseng, M.-C.; Yen, Y.-H.; Chu, Y.-H. Tetrahedron 2004, 60, 12075.

^{215. (}a) Pomeranz, C. *Monatsh* 1893, 14, 116; (b) Fritsch, P. Ber. 1893, 26, 419; (c) Gensler, W.J. Org. React. 1951, 6, 191; (d) Popp, F.D.; McEwen, W.E. Chem. Rev. 1958, 58, 321 (see p 328); (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-75; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 526-527.

^{216.} Herz, W.; Tocker, S. J. Am. Chem. Soc. 1955, 77, 6355.

isoquinoline **319**.²¹⁷ The yield of **319** was only 15% by the Pomeranz-Fritsch method, but 40% with this variation known as the **Schlittler-Müller modification**.²¹⁷



The Pomeranz-Fritsch and Schlittler-Müller disconnections are



12.5.C. Synthesis of Acridines, Carbazoles, and Phenanthridines

Acridines are useful and medicinally important compounds. They can be produced in a straightforward manner by a Friedel-Crafts reaction the **Bernthsen acridine synthesis**,²¹⁸ which couples diaryl amines (such as diphenylamine) with a carboxylic acid (such as benzoic

acid) in the presence of a Lewis acid (zinc chloride is a typical reagent). Heating diphenylamine to 260° C (10 h) with benzoic acid and zinc chloride gave a 48% yield of acridine 320.^{218b}



The carbazole nucleus (carbazole itself is **323**) is also an important structural feature of many alkaloids. The **Borsche-Drechel cyclization**²¹⁹ is a Friedel-Crafts route to these compounds, related to the Fischer indole synthesis discussed in Section 12.5.E. A typical reaction used phenylhydrazone derivatives of ketones such as cyclohexanone phenylhyrazone (**321**), which was cyclized with sulfuric acid to give **322** in good yield. Aromatization with lead oxide (Pb₃O₄) gave **323** in low yield. Glacial acetic acid gave cleaner products in the dehydrogenation step,²²⁰

^{217.} Schlittler, E.; Müller, J. Helv. Chim. Acta 1948, 31, 914, 1119.

 ^{218. (}a) Bernthsen, A. Annalen 1878, 192, 1; (b) Idem Ibid. 1884, 224, 1; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-10.

⁽a) Dreschsel, E. J. Prakt. Chem. 1888, 38, 69; (b) Borsche, W.; Feise, M. Berichte 1907, 40, 378; (c) Campbell, N.; Barclay, B.M. Chem. Rev. 1947, 40, 359 (see p 361); (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-13; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 108-109.

^{220.} Perkin Jr., W.H.; Plant, S.G.P. J. Chem. Soc. 1921, 119, 1825.

but tetrachlorobenzoquinone (also known as chloranil) led to the best yield of 323.221



Phenanthridines can be prepared by modification of the Friedel-Crafts reaction. The **Pictet-Hubert reaction**²²² reacted an acyl *o*-aminobiphenyl (**324**) with zinc chloride at 300°C,²²³ or more commonly with POCl₃ in refluxing nitrobenzene,²²⁴ to give the Friedel-Crafts cyclization



product, phenanthridine **325**. Zinc chloride required long heating and wasteful purification, and gave poor results with reactive substrates. The use of both $POCl_3$ and a high-boiling solvent improved the yields of phenanthridine products.

The disconnections discussed in this section are



12.5.D. Synthesis of Oxygenated Aromatic Derivatives

The **Bradsher reaction** (see **260** in sec. 12.5.A, where X = O) can generate aromatic derivatives containing an oxygen atom in a polycyclic framework. There are also many phenol derivatives, where the oxygen atom is appended to a simple aromatic ring or to polycyclic aromatic compounds. An interesting route to such compounds exploits the propensity of aryls to rearrange under Friedel-Crafts conditions. When a phenolic ester (such as phenyl acetate, **326**) is heated with a Lewis acid such as AlCl₃, a rearrangement occurs to generate an ortho ketone (**330**) and a para ketone (**329**) in what is known as the **Fries rearrangement**.²²⁵

224. Morgan, G.T.; Walls, L.P. J. Chem. Soc. 1931, 2447.

^{221.} Barclay, B.M.; Campbell, N. J. Chem. Soc. 1945, 530.

⁽a) Pictet, A.; Hubert, A. Berichte 1896, 29, 1182; (b) Morgan, C.T.; Walls, L.P. J. Chem. Soc. 1931, 2447;
(c) Idem Ibid. 1932, 2225; (d) Eisch, J.; Gilman, H. Chem. Rev. 1957, 57, 525; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-73; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 506-507.

^{223.} Theobald, R.S.; Schofield, K. Chem. Rev. 1950, 46, 171 (see p 175).

⁽a) Fries, K.; Finck, G. Berichte 1908, 41, 4271; (b) Fries, K.; Pfaffendorf, W. Ibid. 1910, 43, 212; (c) Blatt, A.H. Org. React. 1942, 1, 342; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-35; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 260-261.

reaction generates an acylium ion (327), which fragments to an aluminum alkoxide (328) ionpaired with the acylium ion $MeC=O^+$. Migration and Friedel-Crafts acylation generates both ortho and para products.



This reaction is probably used most often to prepare acetate derivatives,²²⁶ as in the conversion of **331** to **332** in quantitative yield in a synthesis of heliannuol D by Macías and co-workers.²²⁷



The Fries rearrangement is not restricted to acetate unit, however, and other acyl units have been transferred to a aromatic ring.²²⁸ In many cases, there is a regiochemical preference for the para product due to steric

effects that hinder reaction at an available ortho position.²²⁹ When the aromatic ring contains electron-withdrawing groups, the reaction does not work well. A thia-Fries rearrangement of aryl sulfonate esters such as phenyl *p*-toluenesulfonate has been reported.²³⁰ Irradiation of this tosylate with microwaves on silica gel, for 10 min, gave an 87% yield of *o*- and *p*-toluenesulfonyl phenol (80:20). There is also a **photo Fries rearrangement**, which proceeds via radical intermediates formed by the initial photolysis (sec. 11.10.B, for a brief overview of photochemical theory). The ketone is formed from the bis(acyl) derivative under photolytic conditions.²³¹

The Fries rearrangement disconnection is

$$\underset{R}{\overset{O}{\longrightarrow}} \overset{OH}{\longrightarrow} OH + \underset{R}{\overset{OH}{\longrightarrow}} \overset{OH}{\longrightarrow} \overset{OH}{\longrightarrow} OH + RCO_2H$$

Coumarin derivatives (see **336**) can be formed via Friedel-Crafts techniques. The **Pechmann condensation**²³² is illustrated by esterification of phenol with a β -keto-ester (a transesterification reaction), which gave **333**. Subsequent cyclization with AlCl₃ generated coumarin **334**.

- 227. Macías, F.A.; Chinchilla, D.; Molinillo, J.M.G.; Marín, D.; Varela, R.M.; Torres, A. Tetrahedron 2003, 59, 1679.
- 228. For an example see Cairns, N.; Harwood, L.M.; Astles, D.P. Tetrahedron Lett. 1988, 29, 1311.
- 229. Jefferson, A.; Wangchareontrakul, S. Aust. J. Chem. 1985, 38, 605.
- 230. Moghaddam, F.M.; Dakamin, M.G. Tetrahedron Lett. 2000, 41, 3479.
- 231. Anderson, J.C.; Reese, C.B. Proc. Chem. Soc. 1960, 217.
- (a) von Pechmann, H.; Duisberg, C. Berichte 1883, 16, 2119; (b) Sethna, S.; Shah, N.M. Chem. Rev. 1945, 36, 1 (see p 10); (c) Sethna, S.; Phadke, R. Org. React. 1953, 7, 1; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-70; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 490-491.

^{226.} For an example using BF₃ as a catalyst with hydroquinone diester, see Boyer, J.L.; Krum, J.E.; Myers, M.C.; Fazal, A.N.; Wigal, C.T. *J. Org. Chem.* **2000**, *65*, 4712.

Isolation of esters such as **333** is not always necessary and protonic acids can be used. In a synthesis of (+)-aflatoxin B_1 by Trost and Toste,²³³ catechol **335** was condensed with diethyl 3-oxo-1,6-hexanedioate in the presence of ethanolic HCl to give a 47% yield of coumarin **336**. The Pechmann condensation is facilitated by the presence of hydroxyl (OH), dimethylamino (NMe₂) and alkyl groups (R) meta to the hydroxyl of the phenol.^{234,235} Pechmann condensation in an ionic liquid (1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl•2AlCl₃]) using ethyl acetate has also been reported.²³⁶



The Pechmann disconnection is:



12.5.E. Other Aromatic Substitution Reactions. The Fischer Indole Synthesis^{237,240}

This section has been devoted to variations of electrophilic aromatic substitution to make carbon-carbon bonds. There are other alkaloid-forming reactions that do not readily fit into this category, but since they involve acid-catalyzed processes are placed here. The indole nucleus (see **340**) is a component of many natural products and medicinal compounds.²³⁸ In 1883, Fischer reported a straightforward synthesis of indoles that is today considered a powerful reaction (sec. 10.4.B). Although many total syntheses of indole alkaloids begin with indole,

^{233.} Trost, B.M.; Toste, F.D. J. Am. Chem. Soc. 2003, 125, 3090.

^{234.} Shah, M.M.; Shah, R.C. Berichte 1938, 71, 2075.

^{235.} Miyano, M.; Dorn, C.R. J. Org. Chem. 1972, 37, 259.

In bmim chloroaluminate, 1-butyl-3-methylimidazolium chloroaluminate, [bmim]Cl•2AlCl₃: Potdar, M.K.; Mohile, S.S.; Salunkhe, M.M. *Tetrahedron Lett.* 2001, 42, 9285.

^{237. (}a) Fischer, E.; Jourdan, F. Berichte 1883, 16, 2241; (b) Fischer, E.; Hess, O. Ibid. 1884, 17, 559; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-32; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 244-245.

^{238.} For a review of methods for indole ring synthesis, see Gribble, G.W.J. Chem. Soc. Perkin Trans. 1 2000, 1045.

some syntheses prepare the indole nucleus as part of the synthesis and the Fischer indole synthesis remains an important method for the preparation of indoles.²³⁹ A synthesis begins with conversion of an aldehyde or ketone to a phenylhydrazone (ArNHN=CR₂), by treatment with phenylhydrazine. Subsequent treatment with a Lewis acid (zinc chloride is a good choice) or a protonic acid induces a reaction cascade that results in indole 340. The mechanism of this transformation involves formation of a hydrazone that reacts via the N-amino enamine form of the hydrazone (see 337), in what is probably an electrocyclic process analogous to a Claisen rearrangement (sec. 11.12.D) to form 338. The imine nitrogen of 338 attacks an activated C=N (NH reacts with the Lewis acid to form a complex) with concomitant rearomatization of the benzene ring and formation of the five-membered ring that has a NHX group (a protonic acid converts =NH to =NH₂ which gives -NH₂ in **339** whereas reaction with ZnCl₂ would give -NHZnCl₂ in **339**).²⁴⁰ Loss of an ammonium species by what is effectively an E1 process completes the synthesis of the indole ring (340). An application of the Fischer indole reaction is taken from Roberson and Woerpel's synthesis of peduncularine.²⁴¹ In this synthesis, protected acetal 341 was treated with phenylhydrazine•HCl in 4% sulfuric acid. Deprotection of the acetal to the aldehyde allowed the Fischer indole reaction to proceed, catalyzed by the sulfuric acid, to give a 75% yield of the indole product (342).



The cyclization proceeds with reasonable regioselectivity. The ketone moiety in **343** has two α -carbons, and two different enamine structures could be formed as well as two bis(imine) intermediates.²⁴² The final indole products were **344** and **345**. As the concentration of acid catalyst was increased, the yield decreases but the regioselectivity is about the same (2:1 **344/345**).^{242,243} The stereochemical course of the reaction also depends on the stereochemistry of the hydrazone substrate. In another example, hydrazone **346** (with a cisring juncture) was treated with HCl•ether,

^{239.} For a list of other named reactions that produce indoles, see Li, J.-J.; Corey, E.J. Name Reactions in *Heterocyclic Chemistry*, 2005, Wiley Interscience, New Jersey, pp. 99-158.

^{240.} Robinson, B. Chem. Rev. 1969, 69, 227 and references cited therein.

^{241.} Roberson, C.W.; Woerpel, K.A. J. Am. Chem. Soc. 2002, 124, 11342.

^{242.} Bryan Reed, G.W.; Cheng, P.T.W.; McLean, S. Can. J. Chem. 1982, 60, 419.

^{243.} Rashidyan, L.G.; Asratyan, S.N.; Karagezyan, K.S.; Mkrtchyan, A.R.; Sedrakyan, R.O.; Tatevosyan, G.T. Arm. Khim. Zh. 1968, 21, 793 [Chem. Abstr. 71: 21972z, 1969].

in dichloromethane at room temperature to give a 61% yield of **347**.²⁴⁴ Reaction of **346** with 85% sulfuric acid, however, gave a 42% yield of the isomeric **348** and the course of the reaction depended on the acid strength of the medium. When the trans derivative (**349**) was treated with ethereal HCl under the same conditions, 38% of a single product (**350**) was isolated. Treatment with 85% sulfuric acid gave no cyclization, and only unreacted starting material. Treatment with more concentrated acid led to decomposition of the starting material but no cyclization.



The initially formed imine product may be subject to rearrangement under the strongly acidic reaction conditions. Treatment of the phenylhydrazone of cyclopentane carboxaldehyde (**351**) with acetic acid, for example, led to a 90% yield of **353** via the acid catalyzed rearrangement of imine **352**.²⁴⁵ Cyclopentane carboxaldehyde derivatives gave only fused ring indoles, but larger ring carboxaldehydes led to spiro derivatives or mixtures of fused-ring and spirocyclic products.²⁴⁵



^{244.} Freter, K.; Fuchs, V.; Pitner, T.P. J. Org. Chem. 1983, 48, 4593.

^{245.} Rodríquez, J.G.; Benito, Y.; Temprano, E. J. Heterocyclic Chem. 1985, 22, 1207.

The Fisher indole disconnection is

A related route to indolones is the **Stollé synthesis**,²⁴⁶ where a secondary aryl amine such as diphenylamine reacats with a α -chloro acid chloride or a α -bromo acid bromide, to give a α -bromoamide (such as **355**) or a α -chloroamide. Oxalyl chloride can be used, but a more typical example is the reaction of 2-bromopropanoyl bromide with **354** to give **355**. Friedel-Crafts cyclization with AlCl₃ led to the indolone **356**.²⁴⁷



The Stollé disconnection is



There are, of course, other methods to prepare the indole nucleus.^{248,239} A few methods are presented here to illustrate some of the new methodology. In one approach, Barluenga and co-workers treated **357** with *tert*-butyllithium to give **358**.²⁴⁹ Cyclization and elimination gave lithiated indole **359**, which reacted with electrophiles such as 4-chlorobenzaldehyde to give **360** (71% yield). Another approach used α -diazophosphonates. O'Shea and Coleman reported an organolithium addition strategy.²⁵⁰ Nakamura and Ukita²⁵¹ treated 2-aminobenzophenone with triethyl diazophosphonoacetate, in the presence of the rhodium acetate catalyst (see Sect. 13.9), and obtained an 86% yield of **361**. Subsequent treatment with DBU (sec. 2.9.A) led to a 99% yield of indole **362**.

- 250. Coleman, C.M.; O'Shea, D.F. J. Am. Chem. Soc. 2003, 125, 4054.
- 251. Nakamura, Y.; Ukita, T. Org. Lett. 2002, 4, 2317.

^{246. (}a) Stollé, R. Berichte, 1913, 46, 3915; (b) Idem Ibid. 1914, 47, 2120; (c) Idem, J. Prakt. Chem. 1923, 105, 137; (d) Stollé, R.; Bergdoll, R.; Luther, M.; Auerhahn, A.; Wacker, W. Ibid. 1930, 128, 1; (e) Sumpter, W.C. Chem. Rev. 1945, 37, 443 (see p 446).

^{247.} Julian, P.L.; Pikl, J. J. Am. Chem. Soc. 1935, 57, 563.

^{248.} For a review, see Humphrey, G. R.; Kuethe, J. T. Chem. Rev. 2006, 106, 2875.

^{249.} Barluenga, J.; Sanz, R.; Granados, A.; Fañanás, F.J. J. Am. Chem. Soc. 1998, 120, 4865.



Hiroya and co-workers reported a method for the synthesis of indole-2-carboxylates, based on a palladium catalyzed coupling strategy (see sec. 12.7), in a synthesis of duocarmycin SA.^{252a} Coupling methyl propiolate and **363** under what are called **Negishi coupling**^{252b} conditions led to a 69% yield of indole **364**. Palladium catalyzed coupling reactions are discussed in sec. 12.7.



12.6. π -ALLYL PALLADIUM COMPLEXES

There are a number of organometallic compounds that give products from reaction with nucleophiles. In terms of the product, although not necessarily in terms of the formal mechanism, such organometallics effectively function as electrophilic reagents. Palladium salts react with allylic hydrocarbons and with functionalized allylic derivatives to produce π -allyl complexes. These complexes can react with nucleophilic species, including enolate anions, to produce new carbon-carbon bonds.²⁵³ In these reactions, π -allyl palladium complexes function as C^a equivalents; thus they are included in this chapter.

 ⁽a) Hiroya, K.; Matsumoto, S.; Sakamoto, T. Org. Lett. 2004, 6, 2953; (b) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B.I. J. Am. Chem. Soc. 1978, 100, 2254.

^{253.} Poli, G.; Giambastiani, G.; Heumann, A. Tetrahedron 2000, 56, 5959.

12.6.A. The Wacker Process

The first process to be discussed is a traditional one that probably does not proceed via $\alpha\pi$ -complex. The **Wacker process** (or the **Wacker oxidation**) is used in industry to convert ethylene to acetaldehyde using soluble palladium catalysts.²⁵⁴ An example is the reaction of ethylene with cupric chloride (CuCl₂) and palladium chloride (PdCl₂) to give acetaldehyde. Other alkenes can be oxidized to carbonyls as well, as in the conversion of an alkene to a ketone (see Table 12.11).²⁵⁵

$$H_2C = CH_2 \xrightarrow{CuCl_2, PdCl_2} Me \xrightarrow{O}_{H_2O} Me$$

		$\xrightarrow{\text{dCl}_2} \mathbb{R} \xrightarrow{O}_{CF}$	I ₃	
R	<u>Temp. (°C)</u>	Time (min)	% Ketone	
Н	20	5	85	
Me	20	5	90	
<i>n</i> -Pr	20	10	81	
C ₅ H ₁₁	50	30	65	
C ₆ H ₁₃	50	30	42	
C ₈ H ₁₇	70	60	34	
Alkene or Diene	<u>Temp. (°C)</u>	<u>Time (min)</u>	Product	<u>% Yield</u>
CH2=CCH=CH2	80	30	3-Buten-2-one	34
MeCH=CHCH=CH ₂	20	15	2-Pentenal	91
Cyclopentene	30	30	Cyclopentanone	61
Cyclohexene	30	30	Cyclohexanone	65
Vinyl bromide	10	15	Acrolein	98
1-Bromo-1-pentene	50	15	2-Pentanone	61
1-Bromo-2-phenylethene	40	20	Acetophenone	60
Allyl chloride	50	30	Methyl glyoxal	65
Allyl bromide	50	30	Methyl glyoxal	80
[Reproduced with permissi Rüttinger, R.; Kojer, H. An	ion from Smidt, J.; ngew. Chem 1959	Hafner, W.; Jira, I , 71, 176. Copyrig	R.; Sedlmeier, J.; Sie ht 1959 VCH Weinl	eber, R.; neim.]

Table 12.11. Palladium Catalyzed Conversion of Alkenes to Carbonyl Compounds

Both aldehydes and ketones can be formed in moderate to excellent yields. Conjugated dienes such as 1,3-butadiene give conjugated aldehydes under these conditions. Cyclic alkenes give the expected cyclic ketones. Vinyl and allylic halides are converted to the corresponding carbonyl compound.^{256,257} Wacker oxidation has been reported using molecular oxygen. A catalytic

^{254. (}a) Smidt, J.; Hafner, W.; Jira, R.; Sieber, R.; Sedlmeier, J.; Sabel, A. Angew. Chem. Int. Ed. 1962, 1, 80; (b) Jira, R.; Freiesleben W. Organomet. React. 1972, 3, 1; (c) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-98; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 676-677.

^{255.} Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Rüttinger, R.; Kojer, H. Angew. Chem. 1959, 71, 176.

^{256.} Byrom, N.T.; Grigg, R.; Kongkathip, B. J. Chem. Soc. Chem. Commun. 1976, 216.

^{257.} Clement, W.H.; Selwitz, C.M. J. Org. Chem. 1964, 29, 241.

amount of palladium(II) acetate, pyridine, and oxygen converted dodec-1-ene to 2-dodecanone, in up to 70% yield.²⁵⁸ Similarly, cyclopentene was oxidized to cyclopentanone under an oxygen atmosphere using palladium acetate and molybdovanadophosphate on activated carbon.²⁵⁹

The Wacker oxidation can be used with more complex substrates than those shown, or to construct relatively simple fragments as part of a longer synthesis. An example is taken from Simpkins and co-



worker's synthesis of (+)-demethoxyerythratidinone,²⁶⁰ in which the terminal alkene unit in **366** was converted to methyl ketone **367** in 84% yield.

12.6.B. Formation of π -Allyl Palladium Complexes

The Wacker process involved alkenes, but when the alkene has an allylic position, a new type of organometallic can be formed. With palladium reagents, 1-propene reacts to form a π -allyl metal complex such as **368**, stabilized by back-donation from the metal atom. Substitution reaction of this π -allyl complex with a suitable nucleophile will generate the allylic species, **369**, where X is the nucleophile. Early work by Hüttel and Christ,²⁶¹ and also by Volger²⁶² established that π -allyl complexes could be prepared, but often in very poor yield.^{261c} This low yield was probably due to preferential formation and attempted oxidation of a hydropalladium species such as 370 (derived from cyclohexene), which readily decomposed. Heck showed that arylpalladium chlorides added to conjugated dienes.²⁶³ It was later discovered that oxidation of **370** converts it to the more stable halo-bridged dimer (**371**).²⁶⁴ This observation allowed π -allyl palladium complexes to be examined for their synthetic utility. Trost reacted allylic compounds with disodium tetrachloropalladate (Na_2PdCl_4), in the presence of sodium acetate (NaOAc) and acetic acid (AcOH), and found that halogen dimers were formed. The alkene was used in excess, and a ratio of 2:1 alkene/Pd was optimal. A variety of alkenes can be converted to their palladium complex using Trost's conditions, including (Z)-2-pentene, which generated an 87:13 mixture of 372/373 in 83% yield.²⁶⁴

^{258.} Nishimura, T.; Kakiuchi, N.; Onoue, T.; Ohe, K.; Uemura, S. J. Chem. Soc. Perkin Trans. 1 2000, 1915.

^{259.} Kishi, A.; Higashino, T.; Sakaguchi, S.; Ishii, Y. Tetrahedron Lett. 2000, 41, 99.

^{260.} Zhang, F.; Simpkins, N.S.; Wilson, C. Tetrahedron Lett. 2007, 48, 5942...

^{261. (}a) Hüttel, R.; Christ, H. Chem. Ber. 1963, 96, 3101; (b) Idem, Ibid. 1964, 97, 1439; (c) Hüttel, R.; Dietl, H.; Christ, H. Ibid. 1964, 97, 2037; (d) Hüttel, R.; Christ, H.; Herzig, K. Ibid. 1964, 97, 2710; (e) Hüttel, R.; Dietl, H. Ibid. 1965, 98, 1753; (f) Hüttel, R.; Schmid, H. Ibid. 1968, 101, 252.

^{262.} Volger, H.C. Recl. Trav. Chim. Pays-Bas, 1969, 88, 225.

^{263.} Heck, R.F. J. Am. Chem. Soc. 1968, 90, 5542.

^{264.} Trost, B.M.; Strege, P.E.; Weber, L.; Fullerton, T.J.; Dietsche, T.J. J. Am. Chem. Soc. 1978, 100, 3407.



The reaction follows a Markovnikov orientation (see secs. 2.10.A, 6.2.A, 6.3.A), with the removed hydrogen being allylic to the most substituted end (as in the removal of H_a in the

conversion $374 \rightarrow 375$). Addition of cupric chloride (CuCl₂) influences the ratio of the Markovnikov-like to the anti-Markovnikov-like product.²⁶⁴ Palladation of 2-methyl-2-butene (**376**) without CuCl₂ removed



 H_a to give **378** (71% **378** + 29% **377**). Addition of CuCl₂ led to removal of H_b to give 74% of **377** and 26% of **378**.²⁶⁵ The general order²⁶⁴ for removal of allylic protons appears to be CH₃ > CH₂ >> CH. Conformational effects can alter this order or reactivity, however. The syn-complex usually predominates, as in the reaction of 4-methyl-3-heptene to give **375**. Both (*E*)- and (*Z*)-isomers of the alkene led to the syn-isomer **375**, without a trace of the anti-isomer (**379**).



Morehighly substituted alkenes react faster (trisubstituted > disubstituted > monosubstituted),²⁶⁵ as $PdCl_2$ reaction of 4,8-dimethylnona-1,7-diene (**380**) to give**381**. Allylic systemsconjugated to a carbonyl react slower than<math>reaction of 4,8-dimethylnona-1,7-diene (**380**) to give**381**. Allylic systems<math>react slower than

unconjugated alkenes. Conjugated alkenes do react if there is no competition.^{264,266}

^{265.} Hüttel, R.; McNiff, M. Chem. Ber. 1973, 106, 1789.

^{266. (}a) Jones, D.N.; Knox, S.D.J. Chem. Soc. Chem. Commun. 1975, 165; (b) Harrison, I.T.; Kimura, E.; Bohme, E.; Fried, J.H. Tetrahedron Lett. 1969, 1589; (c) Susuki, T.; Tsuji, J. Bull. Chem. Soc. Jpn 1973, 46, 655.

Trost proposed the following mechanism to explain formation of π -allyl complexes from alkenes.²⁶⁴ A mechanism for the palladium-mediated arylation of alkenes by arylmercury compounds had been proposed earlier by Heck.²⁶⁷ Initial reaction with PdCl₄ generates a π -alkene complex (**382**), which is in equilibrium with the π -allyl palladium hydride complex **383**. The presence of a base (such as an amine or a phosphine) or CuCl₂ led to removal of the hydrogen from Pd-H to give the π -allyl palladium dimer **384**. The CuCl₂ oxidative procedure is more efficient than addition of a base.



12.6.C. Reactions of π -Allyl Palladium Complexes

Initial reactions with π -allyl palladium complexes involved treatment with nucleophiles. Heck reported the arylation, methylation, and carboxyalkylation of alkenes by organomercury compounds, mediated by palladium, and other transition metals derivatives.²⁶⁸ Trost found that **385** reacted with diethyl sodiomalonate in the presence of triphenylphosphine (PPh₃). The phosphine acted as a basic ligand, and coordinated with the palladium. The major product from reaction with sodium malonate was **386**, formed in 68% yield.²⁶⁹ This reaction completes the initially set goal (in sec. 12.1) of forming a new carbon bond by reacting a stable cation with a carbon nucleophile. The distribution of products shows a preference for attack at the less substituted carbon [the ratio (386 + 387)/388 was about 8:1, and the ratio 386/387 was 1.6:1]. When **385** reacted with methyl methanesulfonyl sodioacetate (**389**), only one product was observed (390) in 80% yield.²⁶⁹ The extent of attack at the less substituted carbon was dependent on the nature and amount of the added phosphine ligand, as shown in Table 12.12.²⁶⁹ Many common ligands are shown there. It is seen that **391** was converted to the π -allyl complex 392 using various ligands, which then reacted with methyl methanesulfonyl sodioacetate (389) to form a mixture of 393 and 394. A variety of carbanion nucleophiles can be reacted with π -allylpalladium complexes.²⁷⁰



^{267.} Heck, R.F. J. Am. Chem. Soc. 1969, 91, 6707.

270. Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. J. Am. Chem. Soc. 1978, 100, 3426.

^{268.} Heck, R.F. J. Am. Chem. Soc. 1968, 90, 5518.

^{269.} Trost, B.M.; Weber, L.; Strege, P.E.; Fullerton, T.J.; Dietsche, T.J. J. Am. Chem. Soc. 1978, 100, 3416.



Table 12.12. Dependence of Regioselectivity on Ligands in Alkylation of Di-μ-chlorobis (1,2-tetra-methylene-π-allyl)dipalladium (II) with Methyl Methanesulfonyl Sodioacetate

$\begin{array}{c} \begin{array}{c} & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & \\ & $	1aH 389	CO_2Me +		D ₂ Me CO ₂ Me
→391 [[] →392 []]	\bigtriangledown	393	394	
Ligand	Solvent	<u>% Yield</u>	<u>% 393</u>	<u>% 394</u>
Triphenylphosphine	DMSO	75	62	38
	THF	81	89	11
Tributylphosphine	DMSO	100	100	
	THF	57	90	10
dppe [1,2-bis(diphenylphosphino)ethane]	DMSO	64	76	24
	THF	100	75	25
dppp [1,3-bis(diphenylphosphino)propane]	DMSO	100	75	25
	THF	72	78	22
Diphenyl-o-tolylphosphine	DMSO	66	54	46
	THF	53	87	13
TOT [tri-o-tolylphosphine]	DMSO	90	18	82
	DMSO	79	12	18
	THF	0		
Tri-o-anisylphosphine	DMSO	80	70	30
Tri-o-trifluoromethylphosphine	DMSO	79	49	51
HMPT [hexamethylphosphorus triamide]	DMSO	58	100	
	THF	90	100	
Trimethylphosphite	DMSO	91	87	13
	THF	88	91	9
Triphenylphosphite	DMSO	86	93	7
	THF	69	91	9
TMEDA $[N, N, N', N'$ -tetramethylethylenediamine]	DMSO	12	66	34
	THF	17	100	
Triphenylarsine	DMSO	4	62	38
	THF	86	100	
NONE	DMSO	0		
	THF	0		
[Reprinted with permission from Trost, B.M.; Weber, I Soc. 1978, 100, 3416. Copyright © 1978 American Ch	; Strege, P.E.; emical Society.	Fullerton, T.J.; I]	Dietsche, T.J. J.	Am. Chem.

When TOT was used in place of HMPT, the regioselectivity was reversed²⁷⁰ as seen in Table 12.12. The coordinating ligand is critically important, but there does not seem to be a strong solvent effect on the stereochemistry of the reaction. Addition of bis(phosphine) ligands such as bis(diphenylphosphinoethane), dppe, generates a complex **394** rather than the dimeric

palladium chloride structure observed previously. Reaction of **391** with **389** in the presence of dppe gave a 4:1 mixture of **393** and **394**. A synthetic application is Marchand and co-worker's reaction of **395** and the allylic sulfone anion (from **396**) gave a 52% yield of **397**.²⁷¹ Elimination of the sulfone moiety generated vitamin A alcohol **398**.



The π -allyl palladium coupling disconnections are



12.6.D. Catalytic π -Allyl Palladium Reactions

The entire allyl palladium alkylation process discussed in Sections 12.6.A and 12.6.B can be made catalytic in palladium. Indeed, Heck showed that the palladium-catalyzed arylation of enol esters gave aryl-substituted alkenes in modest yield.²⁷² Heck also reported the palladium-catalyzed arylation of allylic alcohols with aryl halides.²⁷³ The basis for this catalytic activity involves the use of an allylic substituted species (**369**, allylic acetate, allylic chloride, etc.) rather than an allylic hydrocarbon. A *tetrakis*-palladium(0) complex (L₄Pd) reacts with the allylic substrate to form a π -allyl palladium complex (**399**). Substitution with a nucleophile generates **400** with liberation of palladium species L₄Pd, which is recycled to react with additional **369**.²⁷⁴

$$\begin{array}{c}
\swarrow X + L_4 Pd \longrightarrow \begin{bmatrix} & & \\ Pd \\ L & L \end{bmatrix} \xrightarrow{\text{Nuc}} & & \\
\begin{array}{c}
\text{Nuc} \\
\text{400} \\
\end{array} + L_4 Pd
\end{array}$$

^{271.} Manchand, P.S.; Wong, H.S.; Blount, J.F. J. Org. Chem. 1978, 43, 4769.

^{272.} Heck, R.F. J. Am Chem .Soc. 1968, 90, 5535.

^{273.} Melplder, J.B.; Heck, R.F. J. Org. Chem. 1976, 41, 265.

⁽a) Trost, B.M.; Verhoeven, T.R. J. Am. Chem. Soc. 1976, 98, 630; (b) Idem Ibid. 1978, 100, 3435; (c) Takahashi, K.; Miyake, A.; Hata, G. Bull Chem. Soc. Jpn. 1970, 45, 230,1183; (d) Trost, B.M.; Verhoeven, T.R. J. Org. Chem. 1976, 41, 3215; (e) Idem J. Am. Chem.Soc. 1980, 102, 4730.

Two of the common Pd(0) catalysts are the commercially available *tetrakis*-(triphenylphosphino) palladium (**401**) and bis[1,2-bis-(diphenylphosphino)ethane] palladium [**402**, i.e. Pd(dppe)₂],

$[Ph_{3}P]_{4} Pd \equiv \frac{Pn_{3}P}{Ph_{3}P} Pd \stackrel{Pd}{\searrow} Pph_{3} Ph \stackrel{Ph}{\searrow} Pd \stackrel{Ph}{\bigotimes} Ph \stackrel{Ph}{\searrow} Pd \stackrel{Ph}{\bigotimes} Ph \stackrel{Ph}{\searrow} Pd \stackrel{Ph}{\bigotimes} Ph \stackrel{Ph}{\searrow} Pd \stackrel{Ph}{\bigotimes} Ph $	– Ph – Ph – Ph – Ph
Ph Ph Ph	Ph

prepared by reduction of palladium acetate $[Pd(OAc)_2]$ inthepresence of triphenyl phosphine or dppe.^{274c,d} The use of these ligands was important to the reactions discussed in with Table 12.12.

12.6.D.i. Reactions with Nucleophiles. Previously, a π -allylic palladium complex was generated by reaction of palladium reagents with allylic hydrocarbons prior to reaction with nucleophiles. In the catalytic version of this reaction, an allylic halide or an allylic acetate is used with a palladium(0) reagent. Why use a palladium complex when enolate alkylation is a well-known process (sec. 9.3.A)? A typical enolate coupling reaction is the conversion of 2-methylcyclopentane-1,3-dione (**403**) to the enolate anion by reaction with NaOH, allowing

reaction with allyl bromide. Under these conditions only 34% of **404** was obtained. When allyl acetate was used in place of allyl bromide in this reaction and *tetrakis*(triphenylphosphino) palladium was used as a catalyst, a 94% yield of



404 was obtained.²⁷⁵ In this reaction, formation of the π -allyl palladium complex facilitated coupling with the nucleophilic enolate derived from **403**, which exhibited poor reactivity in the normal enolate alkylation sequence.

This version of the π -allyl palladium reaction uses an allylic acetate or chloride. The use of the acetate is more common, in part because acetate is a weaker nucleophile than chloride. More recently, methyl carbonate groups have been shown to be good leaving groups in this reaction.²⁷⁶ When it involves a substrate where diastereomeric products can result, the stereochemistry of the nucleophilic displacement is an important issue. The addition of chiral ligands and chiral additives lead to asymmetric induction.^{277,278} Palladium assisted alkylation proceeds with net retention of configuration of the acetate or chloride. The displacement can proceed by an

^{275. (}a) Newman, M.S.; Manhart, J.H. J. Org. Chem. 1961, 26, 2113; (b) unpublished observations of Trost, B.M.; Curran, D. reported in citation 31 of Trost, B.M. Acc. Chem. Res. 1980, 13, 385.

For a –OCO₂Ph leaving group, see Ito, K.; Kashiwagi, R.; Hayashi, S.; Uchida, T.; Katsuki, T. Synlett 2001, 284.

^{277. (}a) Kuwano, R.; Kondo, Y.; Matsuyama, Y. J. Am. Chem. Soc. 2003, 125, 12104; (b) Faller, J.W.; Wilt, J.C. Tetrahedron Lett. 2004, 45, 7613.

⁽a) Evans, P.A.; Uraguchi, D. J. Am. Chem. Soc. 2003, 125, 7158; (b) Evans, P.A.; Leahy, D.K.; Slieker, L.M. Tetrahedron Asymmetry 2003, 14, 3613; (c) Evans, P.A.; Leahy, D.K. J. Am. Chem. Soc. 2000, 122, 5012; (d) López, F.; Ohmura, T.; Hartwig, J.F. J. Am. Chem. Soc. 2003, 125, 3426; (e) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.-a.; Takahashi, S. J. Am. Chem. Soc. 2001, 123, 10405; (f) Ohmura, T.; Hartwig, J.F. J. Am. Chem. Soc. 2001, 123, 10405; (f) Ohmura, T.; Hartwig, J.F. J. Am. Chem. Soc. 2002, 124, 15164; (g) Evans, P.A.; Robinson, J.E.; Baum, E.W.; Fazal, A.N. J. Am. Chem. Soc. 2002, 124, 8782; (h) Bandini, M.; Melloni, A.; Umani-Ronchi, A. Org. Lett. 2004, 6, 3199.
$S_N 2$ '-type displacement with retention of configuration as seen in the conversion of **405** to **406** (99% yield; >50:1 dr), taken from Kündig and co-worker's synthesis of acetoxytubipofuran.²⁷⁹ A variety of active methylene compounds can be used as nucleophiles,²⁸⁰ including enolate

anions.²⁸¹ Intramolecular cyclization is possible when the active methylene compound and an allylic acetate or carbonate is incorporated into the same molecule.²⁸² This reaction has been called **Trost allylation**, or the **Tsuji-Trost reaction**.²⁸³



Trost proposed the following mechanism to account for these catalytic transformations. Reaction of the palladium catalyst with 407 generates π -alkene palladium complex 408. Palladium removes the allylic hydrogen atom, and loss of the acetate moiety gives π -allyl palladium complex 409. Nucleophilic attack at C_a leads to 410, with expulsion of the PdL₂ species, whereas attack at C_b leads to 411. Palladium coordinates on the face of the alkene *distal* to the acetate (distant from the acetate: C_a rather than C_b). Palladium displaces acetate with inversion (408 \rightarrow 409). When the nucleophile displaces the palladium, a second inversion occurs at C_a or C_b, whichever is less sterically hindered, to give a net retention of configuration for the conversion 407 \rightarrow 410 and/or 411.



Trost and Genêt provided another example where an alkene and an aromatic ring were coupled using bis(acetonitrile)palladium chloride to convert **412** to desethylibogamine (**415**).²⁸⁴ Initial reaction of the palladium with the enamine moiety of **412** generated **413**, and cyclization with the allylic amine moiety gave **414**. Sodium borohydride was required to reduce the initially formed palladium chloride species to **415**. Organopalladium catalysts are now common for the

^{279.} Kündig, E.P.; Cannas, R.; Laxmisha, M.; Ronggang, L.; Tchertchian, S. J. Am. Chem. Soc. 2003, 125, 5642.

^{280.} Kazmaier, U.; Zumpe, F.L. Angew. Chem. Int. Ed. 1999, 38, 1468.

^{281. (}a) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Zhu, X.-Z. Org. Lett. 2001, 3, 149; (b) Evans, P.A.; Leahy, D.K. J. Am. Chem. Soc. 2003, 125, 8974; (c) Evans, P.A.; Lawler, M.J. J. Am. Chem. Soc. 2004, 126, 8642.

^{282. (}a) Castaño, A.M.; Méndez, M.; Ruano, M.; Echavarren, A.M. J. Org. Chem. 2001, 66, 589; (b) Zhang, Q.; Lu, X.; Han, X. J. Org. Chem. 2001, 66, 7676.

^{283.} The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-94.

^{284. (}a) Trost, B.M.; Genêt, J.P. J. Am. Chem. Soc. 1976, 98, 8516; (b) Trost, B.M. Tetrahedron 1977, 33, 2615 and citation 10 therein.

coupling reactions of alkenes, alkynes or aryls.²⁸⁵



When chiral ligands are used with the palladium catalyst, good enantioselectivity can be achieved in the alkylation reaction.²⁸⁶ Two common ligands²⁸⁷ are the bis(phosphine) complex from chlorodiphenylphosphine, and optically active amino alcohols such as **416**. Phosphinoester binaphthyls such as **417** have also been used.²⁸⁸ The enantioselectivity can be quite good, as when allylic acetate **418** reacted with diethyl malonate in the presence of **417** and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and LiOAc as additives, to give an 89% yield of **419** with 99% ee.²⁸⁸ The identical reaction with **418**, but using **416** as a ligand gave a 93% yield of **419** but in only 56% ee.²⁸⁷



12.6.D.ii. Palladium Mediated Cyclization Reactions. It is possible to use organopalladium chemistry for intramolecular coupling (cyclization) reactions. Treatment of **420** with the palladium catalyst ($[dba]_3Pd_2$, where dba = dibenzylidene acetone, PhCH=CHCOCH=CHPh)



led to cyclization, and generated the five-membered ring in **421** in 78% yield.²⁸⁹ There is a template effect in the π -allyl palladium reactions²⁹⁰ that can

be exploited to form large rings (sec. 6.6.B). Ester **422** was converted to **423** in 70% yield by this procedure, for example, but the yields have been poor in some cases.²⁹⁰

⁽a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* 1975, 4467; (b) Dieck, H.A.; Heck, R.F. J. Organomet. Chem. 1975, 93, 259; (c) Edo, K.; Yamanaka, H.; Sakamoto, T. *Heterocycles* 1978, 9, 271; (d) Ohsawa, A.; Abe, Y.; Igeta, H. Chem. Lett. 1979, 241.

^{286.} Trost, B.M.; Crawley, M.L. Chem. Rev. 2003, 103, 2921.

^{287.} Gong, L.; Chen, G.; Mi, A.; Jiang, Y.; Fu, F.; Cui, X.; Chan, A.S.C. Tetrahedron: Asymmetry 2000, 11, 4297.

^{288.} Kodama, H.; Taiji, T.; Ohta, T.; Furukawa, I. Tetrahedron: Asymmetry 2000, 11, 4009.

^{289.} Trost, B.M.; Lee, D.C.; Rise, F. Tetrahedron Lett. 1989, 30, 651.

^{290. (}a) Trost, B.M.; Verhoeven, T.R. J. Am. Chem. Soc. 1980, 102, 4743; (b) Idem Ibid. 1977, 99, 3867; (c) Idem Tetrahedron Lett. 1978, 2275.



12.6.D.iii. Palladium-Mediated Arylation Reactions. In the presence of palladium catalysts, enolate anions of malonic esters react with aryl halides to give 2-aryl malonates.²⁹¹ The reaction of diethyl malonate with sodium hydride and bromobenzene, with the palladium(0)

 $\begin{array}{c} \begin{array}{c} \begin{array}{c} CO_{2}Et \\ \hline \\ CO_{2}Et \end{array} \xrightarrow{NaH, PhBr, THF} \\ \hline \\ \hline \\ 2\% Pd(dba)_{2} \\ 4\% P(t-Bu)_{3} \end{array} \begin{array}{c} CO_{2}Et \\ Ph \end{array} \begin{array}{c} \begin{array}{c} CO_{2}Et \\ \hline \\ CO_{2}Et \end{array} \end{array}$

catalyst generated *in situ*, gave an 89% yield of diethyl 2-phenylmalonate (**424**). Similar coupling reactions had been reported earlier, but aryl iodides were the substrates and stoichiometric amounts of copper derivatives were

used.²⁹² Arylation of malonates and cyanoesters was later reported using catalytic amounts of copper derivatives.²⁹³



12.6.D.iv. Trimethylenemethane Equivalents. Palladium catalysts can be used to convert trimethylsilyl allylic acetate **425** to a trimethylene methane equivalent (TMM, **426**). A [3+2]-cycloaddition reaction (sec. 11.11) with alkenes generates cyclopentanes in what is called **quinane annulation**.²⁹⁴ In this reaction, the trimethylsilyl unit is a carbanion equivalent and acetate is a carbocation equivalent. In an example taken from a synthesis of (+)-brefeldin A, Trost and Crawly reacted **425** and **427** in the presence of 2.5 mole % palladium acetate and triisopropyl phosphite [P(O*i*-Pr)₃] (toluene,100°C) to generate **428** in 93% yield (>93:2 dr).²⁹⁵ The reaction is characterized by retention of the geometry of the dipolarophile in the cycloadduct, and proceeds with high diastereoselectivity and good regioselectivity. This reaction can also be applied to the formation of larger rings if a diene is used as the dipolarophile.²⁹⁶ Trost later showed that *Z*-alkenes show greater selectivity in this cyclization process.²⁹⁷ Reagents related to **425** react with aldehydes, as well as alkenes, to produce THF derivatives.²⁹⁸ Alkynes also

^{291.} Beare, N.A.; Hartwig, J.F. J. Org. Chem. 2002, 67, 541.

^{292. (}a) Osuka, A.; Kobayashi, T.; Suzuki, H. Synthesis 1983, 67; (b) Setsune, J.-I.; Matsukawa, K.; Wakemoto, H.; Kitao, T. Chem. Lett. 1981, 367.

^{293.} Okuro, K.; Furuune, M.; Miura, M.; Nomura, M. J. Org. Chem. 1993, 58, 7606.

^{294.} Trost, B.M. Angew. Chem. Int. Ed. 1986, 25, 1.

^{295.} Trost, B.M.; Crawley, M.L. J. Am. Chem. Soc. 2002, 124, 9328.

^{296.} Trost, B.M.; MacPherson, D.T. J. Am. Chem. Soc. 1987, 109, 3483.

^{297.} Trost, B.M.; Yang, B.; Miller, M.L. J. Am. Chem. Soc. 1989, 111, 6482.

^{298. (}a) Trost, B.M.; King, S.A. J. Am. Chem. Soc. 1990, 112, 408; (b) Idem Tetrahedron Lett. 1986, 27, 5971.

react with TMM equivalents to form methylenecyclopentene derivatives.²⁹⁹

When TMM equivalents are tethered to alkenes, intramolecular cyclization generates bicyclic methylenecyclopentane derivatives. Cyclization of **429**, for example, led to a 51% yield of **430** along with 18% of uncyclized triene **431**.³⁰⁰ The cyclization reaction proceeded with excellent diastereoselectivity, as shown. Trost has also examined the attachment of chiral auxiliaries to the alkene partner to give asymmetric induction in reactions with TMM equivalents.²⁹⁶



The disconnections for catalytic allyl palladium reactions are essentially the same as for the uncatalyzed version. A few representative examples are



12.7. NAMED PALLADIUM COUPLING REACTIONS

As organometallic chemistry in general, and organopalladium chemistry in particular, have become more popular, many new reactions have been developed. Several of these are so useful that they have joined the list of named reactions. This section will explore several of named reactions that involve palladium catalysts.

12.7.A. The Heck Reaction

There are several variations of the organopalladium reaction, some involving alkenyl palladium and others σ -palladium complexes. One variation generates the palladium species from a heterocyclic alkene. As mentioned in section 12.6.C and 12.6.D, Heck reported the palladium catalyzed coupling of aryl compounds with alkenes. Heck later showed³⁰¹ that substituted alkenes could be prepared by the palladium-catalyzed coupling of alkenes and aryl halides. This

^{299.} Trost, B.M.; Balkovec, J.M.; Angle, S.R. Tetrahedron Lett. 1986, 27, 1445.

^{300.} Trost, B.M.; Grese, T.A.; Chan, D.M.T. J. Am. Chem. Soc. 1991, 113, 7350.

^{301.} Heck, R.F.; Nolley Jr., J.P. J. Org. Chem. 1972, 37, 2320.

latter transformation is now known as the **Heck reaction**,³⁰² and usually involves the coupling of aryl halides or aryl sulfonate esters with alkenes.³⁰³ As Heck reported, the reaction was discovered independently at about the same time by Mizoroki and co-workers.^{302d,e} The aryl palladium complexes that are formed via oxidative coupling of aryl halides with palladium(0) can undergo the Heck reaction.^{304,305} The reaction proceeds with formation of a palladium species such as **432**, with elimination of palladium to give arylated alkene derivatives.³⁰⁶ Aryl halides differ greatly in their reactivity, ArI being the most reactive followed by aryl bromides. In general, aryl chlorides are very unreactive in the Heck reaction. Coupling occurs with many alkenes and aryl derivatives. Styrene reacted with phenylbis(triphenylphosphino) palladium chloride (**433**), in the presence of triethylamine, to give *trans*-stilbene with loss of the palladium complex **434**.³⁰⁷ The palladium reagent (**433**) was generated *in situ* by reaction of palladium acetate [Pd(OAc)₂] and triphenylphosphine in the presence of iodobenzene.



The reaction is thought to proceed by syn addition of the organopalladium, followed by syn elimination of palladium hydride.³⁰⁷ The use of chiral ligands allows asymmetric induction in some Heck reactions.³⁰⁸ Conjugate addition is usually preferred when the alkene contains an electron-withdrawing group. Without such a group, addition occurs at the less substituted carbon.³⁰⁷ In Ruchirawat and Namsa-aid's³⁰⁹ synthesis of ningalin C, aryl bromide **435** reacted with 3-aryl-1-propene derivative **436** in the presence of Pd(0) to give a 65% yield of **437**. New

- 303. For other reactions of this type, see reference 79, pp 386-392.
- 304. Heck, R.F. Org. React. 1982, 27, 345.

^{302. (}a) See Heck, R.F. *Synlett* 2006, 2855, and the articles in special issue No. 18 of *Synlett*, 2006, 2855-3184;
(b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-42; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 296-297; (d) Mizoroki, T.; Mori, K.; Ozaki, A *Bull. Chem. Soc. Jpn.* 1972, 44, 581; (e) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Jpn.* 1973, 46, 1505.

^{305. (}a) Patel, P.A.; Ziegler, C.B.; Cortese, N.A.; Plevyak, J.E.; Zebovitz, T.C.; Terpko, M.; Heck, R.F. J. Org. Chem. 1977, 42, 3903; (b) Cortese, N.A.; Ziegler Jr., C.B.; Hrnjez, B.J.; Heck, R.F. Ibid. 1978, 43, 2952; (c) Mori, M.; Kudo, S.; Ban, Y. J. Chem. Soc. Perkin Trans 1 1979, 771.

^{306.} For a review of mechanistic considerations for the Heck reaction, see Amatore, C.; Jutland, A. Acc. Chem. Res. 2000, 33, 314.

^{307.} Dieck, H.A.; Heck, R.F. J. Am. Chem. Soc. 1974, 96, 1133.

^{308.} Deng, W.-P.; Hou, X.-L.; Dai, L.-X.; Dong, X.-W. Chem. Commun. 2000, 1483.

^{309.} Namsa-aid, A.; Ruchirawat, S. Org. Lett. 2002, 4, 2633.

catalysts have been developed that allow Heck coupling with deactivated aryl chlorides.³¹⁰ Beller and co-workers showed that chlorobenzene reacted with styrene, for example, to give *trans*-stilbene in 63% yield in the presence of K_2CO_3 and a palladium catalyst having a di(1-adamantyl)-*n*-butylphosphine ligand.³¹⁰ A ligand-free version of the Heck reaction (does not require the use of phosphine ligands) was recently reported, using palladium acetate and potassium phosphate in *N*,*N*-dimethylacetamide.³¹¹ Aryl chlorides undergo the Heck reaction at ambient temperatures, with high selectivity using a Pd/P(*t*-Bu)₃/Cy₂NMe catalyst.³¹²



The intramolecular version of this reaction is well known^{313,314} and quite useful in natural product synthesis, including asymmetric syntheses.³¹⁵ An example of this variation is taken from Enders and co-worker's synthesis of the 1-*epi*-aglycon of the cripowellins A and B,³¹⁶ where palladium catalyzed reaction of **438** with the gave a 59% yield of **439** with >98% de and ee. Other highly enantioselective intramolecular Heck reactions have been reported using a monodentate ligand.³¹⁷



Heterocyclic substrates can be used in the Heck reaction. For example, 2-bromothiophene and 4-vinylpyridine reacted to a give 57% yield of the 2-thiophenyl-4-pyridyl ethene derivative.³¹⁸ In a synthesis of tangutorine by Hsung and co-workers, Heck coupling of bromoindole derivative **440** and methyl acrylate gave an 82% yield of **441**.³¹⁹ The Heck reaction can also be applied to heterocyclic vinyl halides³²⁰ and vinyl triflates. Pure cis or trans alkenes can isomerize to a mixture of cis and trans products.³²⁰ In some cases, however, the selectivity is good as can

- 311. Yao, Q.; Kinney, E.P.; Yang, Z. J. Org. Chem. 2003, 68, 7528.
- 312. Littke, A.F.; Fu, G.C. J. Am. Chem. Soc. 2001, 123, 6989.
- 313. Zhang, Y.; Negishi, E. J. Am. Chem. Soc. 1989, 111, 3454.
- 314. Abelman, M.M.; Oh, T.; Overman, L.E. J. Org. Chem. 1987, 52, 4130.
- 315. Dounay, A. B.; Overman, L. E. Chem. Rev. 2003; 103, 2945.
- Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M.-I.; Runsink, J.; Raabe, G. J. Org. Chem 2005, 70, 10538.
- 317. Imbos, R.; Minnaard, A.J.; Feringa, B.L. J. Am. Chem. Soc. 2002, 124, 184.
- 318. Frank, W.C.; Kim, Y.C.; Heck, R.F. J. Org. Chem. 1978, 43, 2947.
- 319. Luo, S.; Zificsak, C.A.; Hsung, R.P. Org. Lett. 2003, 5, 4709.
- 320. (a) Dieck, H.A.; Heck, R.F. J. Org. Chem. 1975, 40, 1083; (b) Patel, B.A.; Heck, R.F. Ibid. 1978, 43, 3898.

^{310.} Ehrentraut, A.; Zapf, A.; Beller, M. Synlett 2000, 1589.

be seen in Kirschning and co-worker's synthesis of the *N*-acetylcysteamine thioester of secoproansamitocin.³²¹ In this work, vinyl iodide **443** reacted with the terminal alkene moiety of **442** to give a 72% yield of the coupled product **444**, using the so-called **Jeffery protocol**,³²² with high selectivity for the (*E*)- alkene unit of the diene.



There are several variations that involve heteroatom substituents, including biaryl ethers, amines or ketones, which can be coupled to alkenes using palladium acetate.³²³ Medium ring heterocycles can be prepared via an intramolecular Heck reaction.³²⁴ Silyl enol ethers can also be coupled to another alkene upon treatment with palladium acetate to form conjugated ketones.³²⁵ Solvents can change with the reactive partners. Aryldiazonium salts couple to alkenes using palladium acetate in aqueous media.^{326a} Carbohydrate-based vinyl bromides have been coupled to methyl acrylate using Pd(dba)₂ in aqueous DMF.³²⁷ Alkynes have been coupled to pyrrole using Heck-like conditions.³²⁸ Recyclable Pd (II) catalysts with bis(imidazole) ligands, are used with Heck reactions in ionic liquids.³²⁹ A noncatalytic Heck reaction was reported using

322. Jeffery, T. Tetrahedron 1996, 52, 10113.

- 324. Arnold, L.A.; Luo, W.; Guy, R.K. Org. Lett. 2004, 6, 3005.
- 325. Ito, Y.; Aoyama, H.; Hirao, T.; Mochizuki, A.; Saegusa, T. J. Am. Chem. Soc. 1979, 101, 494.
- 326. (a) Sengupta, S.; Bhattacharya, S. J. Chem. Soc. Perkin Trans. 1 1993, 1943; (b) For a Heck coupling with an aryl diazonium salt used in a synthesis of (–)-codonopsinine see Severino, E.A.; Correia, C.R.D. Org. Lett. 2000, 2, 3039; and in a synthesis of the defucogilvocarcin M chromophore, see Patra, A.; Pahari, P.; Ray, S.; Mal, D. J. Org. Chem. 2005, 70, 9017.
- 327. Hayashi, M.; Amano, K.; Tsukada, K.; Lamberth, C. J. Chem. Soc. Perkin Trans. 1 1999, 239.
- 328. Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. Org. Lett. 2000, 2, 2927.
- 329. Park, S.B.; Alper, H. Org. Lett. 2003, 5, 3209.

^{321.} Frenzel, T.; Brunjes, M.; Quitschalle, M.; Kirschning, A. Org. Lett. 2006, 8, 135.

^{323. (}a) Åkermark, B.; Eberson, L.; Jonsson, E.; Pettersson, E. J. Org. Chem. 1971, 40, 1365; (b) Itahara, T.; Sakakibara, T. Synthesis 1978, 607; (c) Itahara, T. Ibid. 1979, 151.

supercritical water as the medium.330

The Heck and related disconnections are



12.7.B. Stille Coupling

Vinyl triflates (C=C-OSO₂CF₃) react with vinyltin derivatives to give dienes, in what is known as the **Stille coupling**.^{331,332} Preparation of vinyl triflate **445** is illustrated by trapping the enolate of 2-methylcyclohexanone (sec. 9.2, 9.3.B) with *N*-phenyl triflimide,³³³ and reaction with vinyltin compound **446** in the presence of a Pd(0) reagent gave diene **447** quantitatively as a 95:5 (*E*,*E*)/(*E*,*Z*) mixture.³³³ Coupling two different alkene units in this way has been referred to as **Stille cross-coupling**, and vinyl iodides are commonly used.³³⁴ The reaction can also be applied to coupling aryl units with vinyl or allylic units. In Phillips and Keaton's synthesis of (–)-7-demethylpiericidin A₁, (**450**),³³⁵ pyridyl-tributyltin **448** was coupled to allylic carbonate **449**, in the presence of Pd₂(dba)₃ to give a 55% yield of **450**. Aryl bromides have been coupled to tributylvinyltin compounds.³³⁶



- 330. Zhang, R.; Zhao, F.; Sato, M.; Ikushima, Y. Chem. Commun. 2003, 1548.
- 331. (a) Scott, W.J.; Crisp, G.T.; Stille, J.K. J. Am. Chem. Soc. 1984, 106, 4630; (b) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-89; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 620-621.
- 332. For reactions involving organotin compounds, see reference 79, pp 434-437.
- 333. McMurry, J.E.; Scott, W.J. Tetrahedron Lett. 1983, 24, 979.
- 334. For the use of a vinyl iodide in a Stille coupling, in a synthesis of elysiapyrones A and B, see Barbarow, J.E.; Miller, A.K.; Trauner, D. *Org. Lett.* **2005**, *7*, 2901.
- 335. Keaton, K. A.; Phillips, A. J. J. Am. Chem. Soc. 2006, 128, 408.
- 336. For an example taken from a synthesis of ageladine A, see Meketa, M.L.; Weinreb, S.M. Org. Lett. 2006, 8, 1443.

Mechanistic rationales for the Stille reaction have been reviewed,³³⁷ and the Stille coupling has been shown to be catalytic in tin.^{338,339} Reaction of alkyne **451** with vinyl bromide **452** in the presence of a palladium catalyst and 6% Me₃SnCl, for example, gave a 90% yield of **453**.³³⁸ This reaction required syringe pump addition of the vinyl bromide over 15 h to the rather complex reaction medium, but the yields were quite good. A method has been developed that allows coupling with aryl chlorides.³⁴⁰ There has been increasing interest in intramolecular Stille reactions in organic synthesis.³⁴¹ An example is taken from Lee and co-workers synthesis of lasonolide A,³⁴² in which **454** was converted to **455** in 55% yield as a 2:1 E/Z mixture.



The Stille coupling disconnections are



12.7.C. Suzuki-Miyaura Coupling

This reaction involves organoboronic acids $[RB(OH)_2]$, so there is a connection with the chemistry presented in chapter 5 for organoboranes. The chemistry involves organopalladium

- 341. For a review, see Duncton, M.A.J.; Pattenden, G. J. Chem. Soc. Perkin Trans. 1 1999, 1235.
- 342. Song, H.Y.; Joo, J.M.; Kang, J.W.; Kim, D.-S.; Jung, C.-K.; Kwak, H.S.; Park, J.H.; Lee, E.; Hong, C.Y.; Jeong, S.W.; Jian, K.; Park, J.H. J. Org. Chem. 2003, 68, 8080.

^{337.} Espinet, P.; Echavarren, A.M. Angew. Chem. Int. Ed. 2004, 43, 4704.

^{338.} Maleczka, Jr., R.E.; Gallagher, W.P.; Terstiege, I. J. Am. Chem. Soc. 2000, 122, 384.

^{339.} The mechanism of the Stille coupling has been studied. See Casado, A.L.; Espinet, P.; Gallego, A.M. J. Am. Chem. Soc. 2000, 122, 11771.

^{340.} Littke, A.F.; Fu, G.C. Angew. Chem. Int. Ed. 1999, 38, 2411.

catalysts so it is related to the Heck reaction and Stille coupling and is presented here as a synthetic route to biaryls.³⁴³

Suzuki and co-workers found that aryl triflates react with arylboronic acids [ArB(OH)₂],³⁴⁴ in the presence of a palladium catalyst, to give biaryls in a reaction that is now known as **Suzuki coupling**³⁴⁵ or **Suzuki-Miyaura coupling**. In an example taken from a synthesis of vialinin A by Takahashi and co-workers, boronic acid **457** reacted with aryl bis(triflate) **456** in the presence of Pd(PPh₃)₄ to give **458** in 96% yield.³⁴⁶ Even hindered boronic acids give good yields of the coupled product.³⁴⁷ The reaction is not restricted to simple aromatic compounds, as illustrated by the reaction of borylated indole **460** with iodopyrazine **459** to give a 76% yield of **461** in Stoltz and co-worker's synthesis of dragmacidin D.³⁴⁸ In addition to boronic acid derivatives, organoboranes react with aryl triflates under these conditions to form biaryls.³⁴⁹ A microwave-promoted Suzuki-type coupling was reported that did not involve the use of transition metal compounds.³⁵⁰



343. For reactions of this type, see reference 79, pp 362-364.

- 345. (a) Miyaura, N.; Suzuki, A. Chem. Rev. 1995, 95, 2457; (b) Farinola, G.M.; Fiandanese, V.; Mazzone, L.; Naso, F. J. Chem. Soc. Chem. Commun. 1995, 2523; (c) Genêt, J.P.; Linquist, A.; Blart, E.; Mouriès, V.; Savignac, M.; Vaultier, M. Tetrahedron Lett. 1995, 36, 1443; (d) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-92; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 636-637.
- 346. Ye, Y.Q.; Koshino, H.; Onose, J.-i.; Yoshikawa, K.; Abe, N.; Takahashi, S. Org. Lett. 2007, 9, 4131.
- 347. (a) Watanabe, T.; Miyaura, N.; Suzuki, A. Synlett 1992, 207; (b) Chaumeil, H.; Signorella, S.; Le Drian, C. Tetrahedron 2000, 56, 9655.
- 348. Garg, N.K.; Sarpong, R.; Stoltz, B.M. J. Am. Chem. Soc. 2002, 124, 13179.
- 349. Fürstner, A.; Seidel, G. Synlett 1998, 161.
- 350. Leadbeaater, N.E.; Marco, M. J. Org. Chem. 2003, 68, 5660.

^{344. (}a) Miyaura, N.; Yanagi, T.; Suzuki, A. Synth. Commun. 1981, 11, 513; (b) Cheng, W.; Snieckus, V. Tetrahedron Lett. 1987, 28, 5097; (c) Badone, D.; Baroni, M.; Cardomone, R.; Ielmini, A.; Guzzi, U. J. Org. Chem. 1997, 62, 7170.

The reaction is not restricted to the formation of biaryls, and there are many synthetic applications.³⁵¹ Aryl boronic acids can also react with vinyl halides and vinyl triflates in the presence of palladium (0). A synthetic example is taken from Felpin and co-worker's synthesis of the isoflavanone, griffonianone D,³⁵² in which **462** reacted with the vinyl iodide unit in **463** to give an 73% yield of coupling product **464**. Another modification uses alkynes as coupling partners. In a synthesis of fiscuseptine,³⁵³ Bracher and Daab coupled aryl iodide **465** with propargyl alcohol, in the presence of the palladium catalyst and CuI, to give an 81% yield of **466**.



Thallium (I) ethoxide³⁵⁴ is known to promote Suzuki-Miyaura cross coupling reactions for vinyl or arylboronic acids with vinyl and aryl halide partners. A mixture of $Pd_2(dba)_3$ and tri-*tert*-butylphosphine has proven to be very effective.³⁵⁵ Nickel on charcoal,³⁵⁶ rhodium catalysts,³⁵⁷ and silver oxide-mediated palladium catalysts³⁵⁸ have also been used. The latter catalyst was effective for the preparation of 4-substituted 2(*5H*)-furanones.³⁵⁹ Palladium-on-carbon was shown to be a reusable catalyst in aqueous media,³⁶⁰ as in the preparation of **464**.

Another variation of this coupling reaction modified the boronic acid moiety. Molander and Rivero have shown the use of potassium trifluoroborates and a palladium catalyst leads to cross coupling reaction with aryl and vinyl halides.³⁶¹ In a synthesis of serofendic acids A and B, Toyota, Ihara and Asano coupled potassium trifluorovinylborate with vinyl bromide **467** to give a 51% yield of **468**.³⁶² Potassium organotrifluoroborates (RBF₃K) are prepared by the

358. Chen, H.; Deng, M.-Z. J. Org. Chem. 2000, 65, 4444.

- 360. Sakurai, H.; Tsukuda, T.; Hirao, T. J. Org. Chem. 2002, 67, 2721.
- 361. Molander, G.A.; Rivero, M.R. Org. Lett. 2002, 4, 107.
- 362. Toyota, M.; Asano, T.; Ihara, M. Org. Lett. 2005, 7, 3929.

^{351.} Kotha, S.; Lahiri, K.; Kashinath, D. Tetrahedron 2002, 58, 9633.

^{352.} Felpin, F.-X.; Lory, C.; Sow, H.; Acherar, S. Tetrahedron 2007, 63, 3010.

^{353.} Bracher, F.; Daab, J. Eur. J. Org. Chem. 2002, 2288.

^{354.} Frank, S.A.; Chen, H.; Kunz, R.K.; Schnaderbeck, M.J.; Roush, W.R. Org. Lett. 2000, 2, 2691.

^{355.} Littke, A.F.; Dai, C.; Fu, G.C. J. Am. Chem. Soc. 2000, 122, 4020.

^{356.} Lipshutz, B.H.; Sclafani, J.A.; Blomgren, P.A. Tetrahedron 2000, 56, 2139.

^{357.} Ueda, M.; Miyaura, N. J. Org. Chem. 2000, 65, 4450.

^{359.} Yao, M.-L.; Deng, M.-Z. J. Org. Chem. 2000, 65, 5034.

addition of inexpensive KHF_2 to organoboron intermediates,³⁶³ and they can be used in several of the applications where boronic acids or esters are used.³⁶⁴



12.7.D. Sonogashira and Stephens-Castro Coupling

Under certain conditions, alkynes can be coupled to aryl halides.³⁶⁵ When aryl halides react with copper acetylides to give 1-aryl alkynes such as **469**, the reaction is known as **Castro**-

Stephens coupling.³⁶⁶ Both aliphatic and aromatic substituents can be attached to the alkyne unit, and a variety of aryl iodides have been used. A palladium-



catalyzed variation is also known in which an aryl halide or a vinyl derivative reacts with a terminal alkyne to give derivatives such as **472**. In this variation, called the **Sonogashira coupling**,³⁶⁷ the reaction is catalyzed by a palladium-copper complex at or near ambient temperatures. In a synthesis of the maduropeptin chromophore aglycon, Inoue, Hirama and co-worker's reacted vinyl triflate **470** and alkyne **471** with palladium(0) in the presence of

^{363. (}a) Vedejs, E.; Chapman, R.W.; Fields, S.C.; Lin, S.; Schrimpf, M.R. J. Org. Chem. 1995, 60, 3020; (b) Vedejs, E.; Fields, S.C.; Hayashi, R.; Hitchcock, S.R.; Powell, D.R.; Schrimpf, M.R. J. Am. Chem. Soc. 1999, 121, 2460.

^{364. (}a) Molander, G.A.; Ito, T. Org. Lett. 2001, 3, 393; (b) Molander, G.A.; Biolatto, B. Org. Lett. 2002, 4, 1867; (c) Molander, G.A.; Biolatto, B. J. Org. Chem. 2003, 68, 4302; (d) Molander, G.A.; Katona, B.W.; Machrouhi, F. J. Org. Chem. 2002, 67, 8416; (e) Molander, G.A.; Yun, C.; Ribagorda, M.; Biolatto, B. J. Org. Chem. 2003, 68, 5534; (f) Molander, G.A.; Ribagorda, M. J. Am. Chem. Soc. 2003, 125, 11148.

^{365.} For reactions of this type, see reference 79, pp 596-599.

^{366. (}a) Castro, C.E.; Stephens, R.D. J. Org. Chem. 1963, 28, 2163; (b) Stephens, R.D.; Castro, C.E. J. Org. Chem. 1963, 28, 3313; (c) Sladkov, A.M.; Ukhin, L.Yu.; Korshak, V.V. Bull. Acad. Sci. USSR., Div. Chem. Sci. 1963, 2043; (d) Sladkov, A.M.; Gol'ding, I.R. Russ. Chem. Rev. 1979, 48, 868; (e) Bumagin, N.A.; Kalinovskii, I.O.; Ponomarov, A.B.; Beletskaya, I.P. Doklad. Chem. 1982, 265, 262; (f) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-16; (g) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd ed., Wiley-Interscience, New Jersey, 2005, pp. 136-137.

^{367. (}a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* 1975, 4467; (b) Sonogashira, K. in *Comprehensive Organic Synthesis*, Trost, B.M.; Fleming, I. (Eds.), Pergamon Press, New York, 19991, Vol. 3, chapter 2.4; (c) Rossi, R.; Carpita, A.; Bellina, F. *Org. Prep. Proceed. Int.* 1995, 27, 127; (d) Sonogashira, K. in *Metal-Catalyzed Cross-Coupling Reactions*, Diederich, F.; Stang, P.J. (Eds.), Wiley-VCH, New York, 1998, chapter 5; (e) The Merck Index, 14th ed., Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-88; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. *Name Reactions and Reagents in Organic Synthesis, 2nd ed.*, Wiley-Interscience, New Jersey, 2005, pp. 612-613.

cuprous iodide to give 472.³⁶⁸ Several new reaction variations have brought renewed attention to the coupling. A copper-free Sonogashira coupling has been reported in an ionic liquid medium.³⁶⁹ A combination of Pd(PhCN)₂Cl₂ and $(t-Bu)_3P$ is very effective for Sonogashira coupling at room temperature,³⁷⁰ and the reaction has been done without solvent, on alumina, using microwave irradiation.³⁷¹



12.8. π -ALLYL NICKEL COMPLEXES

Nickel can stabilize allylic cations in a manner similar to palladium.³⁷² Indeed, the use of organonickel complexes for generating carbon-carbon bonds³⁷³ is synthetically older than

the analogous organopalladium chemistry. Nickel chloride (NiCl₂) is the nickel analog of PdCl₂ and reacts similarly to form zero-valent complexes [Ni(0)], which are the reactive species in π -allyl nickel complexes



such as **473**. A common Ni(0) complex is nickel tetracarbonyl $[Ni(CO)_4]$, but this is a volatile, *extremely toxic* and dangerous material.

Nickel tetracarbonyl should be used with **great caution** and only in a specially ventilated hood.



Tetrakis(triphenoxyphosphino)nickel is also a useful organonickel reagent. The *bis*-complex of nickel and cyclooctadiene (cod) **474** [Ni(cod)₂], bis(diphenyl-phosphinoethane)nickel chloride (**475**) and tetraphenyl-nickel (**476**) are widely used Ni(0) complexes.

- 369. Fukuyama, T.; Shinmen, M.; Nishitani, S.; Sato, M.; Ryu, I. Org. Lett. 2002, 4, 1691.
- 370. Hundertmark, T.; Littke, A.F.; Buchwald, S.L.; Fu, G.C. Org. Lett. 2000, 2, 1729.
- 371. Kabalka, G.W.; Wang, L.; Namboodiri, V.; Pagni, R.M. Tetrahedron Lett. 2000, 41, 5151.
- 372. For reactions of this type, see reference 79, pp 116-117.
- 373. For a review, see Montgomery, J. Acc. Chem. Res. 2000, 33, 467.

^{368.} Komano, K.; Shimamura, S.; Inoue, M.; Hirama, M. J. Am. Chem. Soc. 2007, 128, 14184.

A typical reaction involving nickel(0) treats an allylic halide such as 3-chloro-2-methyl-1propene with Ni(CO)₄ to form 477,³⁷⁴ a nickel dimer analogous to the palladium chloride dimer discussed in the previous section. This complex reacts with an alkene to form a new complex (478), and subsequent reaction with a variety of electrophilic reagents removes nickel. In this example, the chlorine was converted to an acetate ligand (in 479) and reacted with methanolic carbon monoxide to give the ester (480).³⁷⁴



 $\begin{array}{c} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ NiCl_{2} \\ \hline \\ PhMgBr \\ SMe \end{array} \begin{array}{c} 0.1 \text{ (diphos)} \\ \hline \\ NiCl_{2} \\ \hline \\ PhMgBr \\ SMe \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ PhMgBr \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \\ Ph \end{array} \begin{array}{c} n-C_{6}H_{13} \\ \hline \end{array} \end{array}$

phenylmagnesium bromide and bis(diphenylphosphinoethane)nickel chloride.³⁷⁵ Zero-valent nickel can also catalyze the coupling of aryl halides and alkenes.^{376,375a,b}

Anickel-catalyzed ene cyclization (sec. 11.13) has been reported that uses Ni(cod)₂. The reaction proceeds by initial formation of a π -allylnickel complex, which facilitates the intramolecular ene reaction with an allylic amine unit.³⁷⁷ π -Allylnickel complexes can be used in coupling reactions with both aryl and alkyl halides. Enolate anions react with nickel(0) reagents to form a complex that subsequently couples to aryl iodides. Semmelhack's final step in the



synthesis of cephalotaxinone (484) treated 483 with $Ni(cod)_2$ to produce 484 in 94% yield.³⁷⁸ The nickel coupling reaction is not limited to aryl halides. Alkyl halides also react, as seen in Marshall and Wuts'

377. Oppolzer, W.; Bedoya-Zurita, M.; Switzer, C.Y. Tetrahedron Lett. 1988, 29, 6433.

^{374. (}a) Gallazzi, M.C.; Hanlon, T.L.; Vitulli, G.; Porri, L. J. Organomet. Chem. 1971, 33, C45; (b) Hughes, R.P.; Powell, J. Ibid. 1971, 30, C45; (c) Guerrieri, F.; Chiusoli, G.P. Ibid. 1968, 15, 209.

^{375. (}a) Wenkert, E.; Ferreira, T.W.; Michelotti, E.L. J. Chem. Soc. Chem Commun. 1979, 637; (b) Wenkert, E.; Michelotti, E.L.; Swindell, C.S. J. Am. Chem. Soc. 1979, 101, 2246.

^{376.} Mori, M; Ban, Y. Tetrahedron Lett. 1976, 1803, 1807.

^{378.} Semmelhack, M.F.; Chong, B.P.; Stauffer, R.D.; Rogerson, T.D.; Chong, A.; Jones, L.D. J. Am. Chem. Soc. 1975, 97, 2507.

coupling of 485 with the π -allyl nickel dimer 486 to give dictyolene 487.³⁷⁹



The nickel(0) coupling disconnections are:

$$\begin{array}{c} R \\ R^{1} \\ R^{1} \\ Nuc \end{array} \xrightarrow{R} \\ R^{1} \\ X \\ R^{1} \\ X \\ Y \\ \end{array} \xrightarrow{R} \\ R^{2} \\ R^{3} \\ R^{3} \\ R^{1} \\ X \\ R^{1} \\ X \\ R^{2} \\ \end{array} \xrightarrow{R} \\ R^{1} \\ R^{2} \\ R^{2} \\ R^{3} \\ R^{1} \\ X \\ R^{2} \\ R^{3} \\ R^{$$

Zero-valent nickel is especially effective for the cyclization of *bis*(allyl) bromides.^{380,381} Corey used this technique to cyclize **488** to **489**. Subsequent photolysis in the presence of diphenyl disulfide (PhSSPh) gave humulene, **490**.³⁸⁰ Wender et al. reported a novel [4+4]-cycloaddition reaction in which two diene moieties are coupled with a nickel(0) catalyst to form eight-membered rings.³⁸² In a synthesis of asteriscanolide, **491** was converted to **492** in 67% yield using the nickel cyclooctadiene catalyst (**474**), with < 5% of the [4+2]-cycloaddition product.³⁸² In this particular case, attempts to use a palladium-catalyzed reaction gave poor yields, presumably due to instability of the vinyl iodide intermediates.



The nickel catalyzed cyclization disconnections are



- 379. Marshall, J.A.; Wuts, P.G.M. J. Am. Chem.Soc. 1978, 100, 1627.
- 380. (a) Corey, E.J.; Hamanaka, E. J. Am. Chem. Soc. 1967, 89, 2758; (b) Idem Ibid. 1964, 86, 1641; (c) Corey, E.J.; Wat, E.K.W. Ibid. 1967, 89, 2757.
- 381. Corey, E.J.; Kirst, H.A. J. Am. Chem. Soc. 1972, 94, 667.
- 382. Wender, P.A.; Ihle, N.C.; Correia, C.R.D. J. Am. Chem. Soc. 1988, 110, 5904.

12.9. ELECTROPHILIC IRON COMPLEXES

12.9.A. Alkene and Diene Iron Complexes

In iron reactions where the reagent was equivalent to C^d, described in Section 8.9.A, the iron moiety was used as an auxiliary. Iron can also stabilize cations, which then react with nucleophiles to generate new carbon-carbon bonds.³⁸³ These cations are formed as iron-alkene complexes, usually by reaction of cyclopentadienyl dicarbonyl ferrate anion (**494**) with an allylic halide such as 3-chloro-2-methyl-1-propene. The initial product in this case was the σ -iron adduct (**495**). Subsequent reaction with an acid generated the π -iron complex **496**, where the double bond was a two- π -electron donor.³⁸⁴ An alternative preparation treated an alkyl cyclopentadienyl dicarbonyl ferrate (**Fp**) complex (such as **497**) with trityl cation (Ph₃C⁺) to form **498**.³⁸⁵

$$\begin{array}{c} & & & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & & \\ & & & \\ & & & &$$

Diene complexes can also be formed by reaction iron pentacarbonyl $[Fe(CO)_5]$.³⁸⁶ The presence and nature of the substituents on the diene will influence the regiochemical outcome of the complex, as does the method of preparation. Treatment of **499** with iron pentacarbonyl under thermal conditions, for example, gave a 4:1 mixture of **500** and **501**, with greater selectivity for reaction at the unhindered face. Photolysis, however, led to a 1:1 mixture of **500** and **501**.³⁸⁷ Treatment of an unconjugated dienes with iron pentacarbonyl led to conjugated dienyl complexes, which were converted to the isomeric π complexes with trityl cation.³⁸⁸



^{383.} For reactions of this type, see reference 79, p 445.

- 386. (a) Whitesides, T.M.; Arhart, R.W. Inorg. Chem. 1975, 14, 209; (b) Brookhart, M.; Whitesides, T.M.; Crockett, J.M. Ibid. 1976, 15, 1550; (c) Whitesides, T.M.; Arhart, R.W.; Slaven, R.W. J. Am. Chem. Soc. 1973, 95, 5792; (d) Impastato, F.J.; Ihrman, K.G. Ibid. 1961, 83, 3726.
- 387. (a) McArdle, P.; Higgins, T. Inorg. Chim. Acta 1978, 30, L303; (b) Davies, S.G. Organotransition Metal Chemistry: Applications to Organic Synthesis, Pergamon Press, Oxford, 1982, p 54.
- 388. (a) Birch, A.J.; Chamberlain, K.B. Org. Synth. Coll. Vol. 6 1988, 996; (b) Birch, A.J.; Cross, P.E.; Lewis, J.; White, D.A.; Wild, S.B. J. Chem. Soc. A 1968, 332; (c) Birch, A.J.; Williamson, D.H. J. Chem. Soc. Perkin Trans. 1 1973, 1892.

^{384.} Green, M.L.H.; Nagy, P.L.I. J. Chem. Soc. 1963, 189.

^{385. (}a) Green, M.L.H.; Nagy, P.L.I. J. Organomet. Chem. 1963, 1, 58; (b) Laycock, D.E.; Hartgerink, J.; Baird, M.C. J. Org. Chem. 1980, 45, 291.

12.9.B. Reactions of Iron Complexes with Nucleophiles



Alkyl iron complexes behave as electrophiles in the presence of nucleophiles. Rosenblum and Rosan showed that the ethene complex of cyclopentadienyl dicarbonyl iron (abbreviated as \mathbf{Fp}), Fp-ethene (**498**),

reacted with dimethyl lithiomalonate to give **502**.³⁸⁹ Conjugated iron complexes can also be prepared.³⁸⁸ These Fp-alkene complexes react with a variety of other nucleophiles,³⁹⁰ including water, alcohols, amines,³⁹¹ phosphines or thiols as well as carbon nucleophiles (enamines, organocuprates, enolates),^{392,393} and dialkyl cadmium reagents.³⁹⁴ Diene complexes such as **503** were converted to the corresponding cationic complexes (**504**) and reaction with malonate gave **505**. The iron complex was removed with trimethylamine *N*-oxide (Me₃N–O) to give **506**.³⁹⁵



The iron carbonyl unit is a protecting group for dienes. Iron diene complex **507**,³⁹⁶ for example, reacted with **508** in a Mukaiyama aldol reaction (sec. 9.4.C) to give an 81% yield of **509** and **510** in an 84:16 ratio. In a synthesis of heptitol derivatives,³⁹⁷ Pearson and Katiyan protected tropone as the iron tricarbonyl derivative (**511**), and prepared **512** using a multistep sequence

- 391. Berryhill, S.R.; Rosenblum, M. J. Org. Chem. 1980, 45, 1984.
- 392. (a) Reference 390, p 132; (b) Busetto, L.; Palazzi, A.; Ros, R.; Belluco, U. J. Organomet. Chem. 1970, 25, 207; (c) Lennon, P.; Madhavarao, M.; Rosan, A.; Rosenblum, M. Ibid. 1976, 108, 93.
- 393. Reference 390, p 142.
- 394. Bayoud, R.S.; Biehl, E.R.; Reeves, P.C. J. Organomet. Chem. 1979, 174, 297.
- 395. Pearson, A.J. J. Chem. Soc. Perkin Trans. 1 1979, 1255.
- 396. Harvey, D.F.; Selchau, V.B. J. Org. Chem. 2000, 65, 2282.
- 397. Pearson, A.J.; Katiyar, S. Tetrahedron 2000, 56, 2297.

^{389.} Rosan, A.; Rosenblum, M. J. Org. Chem. 1975, 40, 3621.

^{390.} Davies, S.G. Organotransition Metal Chemistry: Applications to Organic Synthesis, Pergamon Press, Oxford, 1982.

before deprotecting the diene to give 513.



12.10. CONCLUSION

This chapter discussed chemical equivalents for C^a , cations and organometallics. Although carbocations are subject to racemization and rearrangement, they can be stabilized so they can react with carbon nucleophiles ranging from alkenes and alkynes, to aromatic compounds, to Grignard reagents or enolate anions. Cations can be used synthetically for intramolecular coupling and/or if a tertiary or oxygen stabilized cation is generated. The Friedel-Crafts reactions are among the more powerful and useful of all organic reactions for constructing carbon-carbon bonds when aromatic nuclei are involved. The more recent contributions of metal stabilized cations, including π -allylpalladium, π -allylnickel, π -allyliron and other organometallic reagents allow nucleophiles such as Grignard reagents and enolate anions to be coupled with those C^a species.

In Chapter 13, methods for generating carbon-carbon bonds via radical intermediates and carbones will be discussed, completing the collection of chapters for generating carbon-carbon bonds in organic synthesis.

HOMEWORK

- 1. Friedel-Crafts alkylation is not a useful synthetic method for the synthesis of primary arenes such as 1-phenylhexane. Explain why not.
- 2. Briefly explain the regioselectivity for this reaction.



3. Provide a mechanistic rationale for the following transformation:



4. Offer a mechanistic rationale for the following transformation:



5. Give a mechanistic rationale for the following transformation:



6. Give a mechanistic rationale for this transformation:



7. Give the complete mechanism for the following transformation.



8. What are the mechanistic implications of the following experiment? Of what possible value is this experiment to synthesis if the $R-NH_2 \rightarrow R-OH$ transformation is planned?



9. Give the complete mechanism for the following transformation.



10. Explain the fact that Wolff-Kishner reduction of A gave B but Clemmenson reduction of A gave C.



11. Give a reasonable mechanism for the following transformation.



12. Provide a mechanism for the following transformation:



13. For each of the following, give the major product. Show the correct stereochemistry where appropriate.







14. In each case give a complete synthesis of the target from the designated starting material. Show all intermediate products and give all reagents.



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chapter 13 Carbon Radical Disconnect Products: Formation of Carbon-Carbon Bonds via Radicals and Carbenes

Carbanion reagents, electrophilic reagents and molecules that undergo pericyclic reactions are important for the formation of carbon-carbon bonds. Reactions that involve radical intermediates (molecules that possess a single electron in a reactive orbital) are also important. When a C–C bond is disconnected, ionic disconnect products C^a or C^d may occasionally lead to synthetic equivalents that are either impractical, or have side reactions that are intolerable. A useful alternative disconnect product may be a radical that can be represented as C[•]. Radical reactions have become an important and largely controllable synthetic tool in recent years, and should be considered as an important part of synthetic planning. Carbenes are also important for generating carbon-carbon bonds, and they are included in this chapter. This chapter will discuss methods for preparing radicals and carbenes as well as their applications to synthesis.

13.1. INTRODUCTION



 $\begin{bmatrix} & & \\ &$

trigonal planar carbon with an empty p orbital (2). A radical, which contains one electron in an orbital, can be tetrahedral, planar or 'in between' with properties of both a carbanion and a carbocation. As shown in 3, a reasonable 'in between' structure is a flattened tetrahedron (the actual structure of radicals will be discussed below). In terms of its reactivity, radical 3 could be considered electron rich or electron poor. In most of its reactions, the electron-deficient characterization is useful for predicting products.

Gomberg was the first to characterize a free radical when, in 1900, he generated triphenylmethyl radical 2 4 by reacting chlorotriphenylmethane with zinc metal.¹ Triphenylmethyl radical is unusual in that it is

$$Ph - C - Cl \xrightarrow{Zn^{\circ}} Ph - C \xrightarrow{Ph} + ZnCl_{2}$$

quite stable, and its formation is probably the first experimental verification of a free radical. Frankland, however, may have been the first to generate transient methyl and ethyl radicals

^{1. (}a) Gomberg, M. J. Am. Chem. Soc. 1900, 22, 757; (b) Idem Chem. Ber. 1900, 33, 3150.

in the reaction of iodomethane and iodoethane with zinc in 1849.² A good deal of attention is now focused on the reactivity and applications of radicals to organic synthesis. Excellent monographs by Davies and Parrott,³ Lazár et al.,⁴ Hay,⁵ Giese,⁶ Kochi,⁷ Togo,⁸ Zard⁹ or Renaud and Sibi,¹⁰ describe radical chemistry in great detail, as well as the many applications to synthesis. A review by Curran¹¹ placed an emphasis on synthetic applications.

13.2. STRUCTURE OF RADICALS

As mentioned in the introduction, there are several possible structures for a radical. The two most common are pyramidal (see **3**) and planar (see **7**). Formation of pyramidal radical **3** "involves a transition state that differs from the original molecules only in the length of the central bond", represented by **5**.¹² Dissociation to a planar radical (**7**) is also possible, but requires transition state **6** where both fragments are flattened.¹² Transition state **6** is generally favored over **5**, where **5** represents an "instantaneous bond dissociation". The lower energy dissociation of the molecule, in the transition state prior to cleavage, is graphically presented in Figure 13.1.¹³ For **path 1b**, the C–C bond is changing from C^{sp3}–C^{sp3} to C^p–C^p, which is facile. Formation of the C–R bond is bond strengthening, and energy is released as the radical changes from a pyramidal structure to the planar arrangement. **Path 1a** is the instantaneous bond dissociation, and does not possess as much stabilizing energy. Note that if flattening in **6** is hindered by large steric interactions, then E_{act} increases and in those cases **3** may be the intermediate.



We can use the methyl radical (H₃C•) to begin a discussion of the properties and structure of free radicals. Structure **3** (R = H) represents the ground state of the radical, experimentally

- 7. Kochi, J.K. (Ed.) Free Radicals, Volumes 1 and 2, Wiley, New York, 1973.
- 8. Togo, H. Advanced Free Radical Reactions for Organic Synthesis Elsevier, Amsterdam, 2004.
- 9. Zard, S.Z. Radical Reactions in Organic Synthesis, Oxford University Press, Inc., New York, 2003.

^{2.} Frankland, E. Annalen 1849, 71, 171, 213.

^{3.} Davies, D.I.; Parrott, M.J. Free Radicals in Organic Synthesis Springer-Verlag, Berlin, 1978.

^{4.} Lazár, M.; Rychlý, J.; Klimo, V.; Pelikán, P.; Valko, L. Free Radicals in Chemistry and Biology, CRC Press, 1989.

^{5.} Hay, J.M. Reactive Free Radicals, Academic Press, London, 1974.

^{6.} Giese, B. Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds, Pergamon Press, Oxford, 1986.

^{10.} Renaud, P.; Sibi, M.P. (Eds.), *Radicals in Organic Synthesi, Volume 1. Basic Principles, Volume 2. Applications*, Wiley-VCH, Weinheim and New York, **2001**.

^{11.} Curran, D.P. Synthesis 1988, 417, 489.

^{12.} Reference 5, p 42.

^{13.} Reference 5, p 43.

determined to be planar or nearly so.¹⁴ The inversion energy for the methyl radical has been estimated to be only 4.2 kcal mol⁻¹ (17.6 kJ mol⁻¹).¹⁵ As the temperature increases, the pyramidal model (7, R = H) explains the ¹H and ¹³C NMR as well as the electron spin resonance (ESR) spectra.¹⁶ Three factors control the configuration of a radical: "(*a*) the energy of the unpaired electrons, (*b*) the energies of the bond in the radical and (c) the H–H interaction,¹⁷ which is illustrated by a **Walsh diagram**,¹⁸ shown in Figure 13.2 for the methyl radical".¹⁷ The total energy for inversion supports a double barrier for inversion between the two pyramidal forms, proceeding through the planar form (see the total energy curve in Figure 13.2). The energy of the most stable configuration of the methyl radical was calculated to be about 5 kcal mol⁻¹ (20.9 kJ mol⁻¹),¹⁴ and the energy of the pyramidal methyl was calculated to be about 10 kcal mol⁻¹ (41.9 kJ mol⁻¹) higher than the ground state.^{17,19}



Figure 13.1 Energy Diagram For Dissociation Figure 1 to Planar and Pyramidal Radicals.

Figure 13.2. Walsh Diagram For Inversion of the Pyramidal Methyl Radical.

13.3. FORMATION OF RADICALS BY THERMOLYSIS

Radicals can be formed in several ways. Many involve dissociative **homolytic cleavage** (one electron is transferred to each adjacent atom from the bond) as a key step, as depicted by X-Y that gives two radical products. Another major route to radical intermediates involves the reaction of a radical (X[•]) and a neutral molecule (X–Y), producing a new radical (Y[•]) and a

^{14. (}a) Fessenden, R.W.; Schuler, R.H. J. Chem. Phys. 1963, 39, 2147; (b) Herzberg, G. Proc. R. Soc. London, A 1961, 262, 291.

^{15.} Andrews, L.; Pimentel, G.C. J. Chem. Phys. 1967, 47, 3637.

^{16.} Chang, S.Y.; Davidson, E.R.; Vincow, G. J. Chem. Phys. 1970, 52, 5596.

^{17.} Reference 5, p 45.

^{18.} Walsh, A.D. J. Chem. Soc. 1953, 2288, 2306, 2325.

^{19.} Kibby, C.L.; Weston Jr., R.E. J. Am. Chem. Soc. 1968, 90, 1084.

new neutral molecule (X–X). This latter pathway will be discussed under radical reactions in section 3.5. The equilibrium constant for these processes depends on both the relative bond strength of X–Y and also on the relative stabilities of X• and Y•. For homolytic cleavage, raising the temperature of the reaction will generally shift the equilibrium toward a higher concentration of free radicals.²⁰ This equilibrium

$$\widehat{X} - \widehat{Y} \rightleftharpoons X^{\bullet} + Y^{\bullet} \qquad \widehat{X}^{\bullet} \widehat{X} - \widehat{Y} \rightleftharpoons X - X + Y^{\bullet}$$

makes it convenient to correlate homolytic cleavage with bond dissociation energy. Lazár²¹ published a table of bond energies, in ascending order of bond strength,^{20,22} that correspond to the instantaneous bond dissociation energies (*D*). In principle, lower bond dissociation energies should correlate with an increased propensity for homolytic cleavage. Dissociation of C–C (85 kcal mol⁻¹; 357 kJ mol⁻¹),²¹ C–O (84 kcal mol⁻¹; 351 kJ mol⁻¹),¹⁸ H–O (111 kcal mol⁻¹; 464 kJ mol⁻¹),²¹ and C-halogen bonds (55 kcal mol⁻¹ for C–I to 79.8 kcal mol⁻¹ for C–Cl; 230 kJ mol⁻¹ to 351 kJ mol⁻¹)²¹ all require high reaction temperatures for homolytic cleavage. Alkali metals (K–K, Na–Na, Li–Li) with bond dissociation energies of 55, 69 and 103 kcal mol⁻¹, respectively (229.9, 188.4 and 430.5 kJ mol⁻¹),²¹ undergo homolytic cleavage under very mild reaction conditions. The potent electron-transfer capabilities of these metals for dissolving metal reductions were discussed in Section 4.9. Particularly weak bonds that are expected to give homolytic cleavage are the peroxide bond (O–O, 140 kcal mol⁻¹)²¹ and those of the halogens, which is reflected in the chemical methods used to generate organic radicals. The methods usually begin with thermolysis of peroxides (H₂O₂, ROOR, etc.), diazo compounds (RN₂), or halogens.

Peroxides are potentially dangerous compounds because many of them can detonate upon exposure to heat or light, or under conditions where there is friction or shock. Peroxides are known to oxidize alkenes to oxiranes (especially in the presence of transition metals, see sec. 3.4.B), but if heated they decompose to hydroxy radicals (HO•) or alkoxy radicals (RO•). Lazár et al. published a table of approximate decomposition temperatures for several common peroxides.²³ Hydrogen peroxide requires the rather high temperature of 380°C for a decomposition half-life of 1 h,²³ and it is not very soluble in organic solvents. Peroxide **8**, however, decomposes at such a low temperature $(-16^{\circ}C)^{23}$ that controlling the reaction is difficult in most instances. Benzoyl peroxide (**9**) cleaves at about 95°C,²³ a temperature that is compatible with many organic reactions, allowing some control of the reaction, and is reasonably soluble in organic solvents. Di-*tert*-butyl peroxide (**10**) decomposes at about 150°C²³ to produce Me₃C–O•. Although this peroxide is a useful radical initiator, the higher temperature required for decomposition can occasionally causes problems.

^{20.} Reference 4, p 8.

^{21.} Reference 4, p 9.

^{22. (}a) Sanderson, R.T. Chemical Bonds and Bond Energies, Academic Press, New York, 1976; (b) Idem J. Am. Chem. Soc. 1983, 105, 2259.

^{23.} Reference 4, p 12.



tert-Butyl hydroperoxide (11) is another useful peroxide that decomposes to give Me₃C–O•, 12, and water. The presence of a α -hydrogen, as in diisopropyl peroxide (13), increases the facility of additional decomposition reactions. Initial homolytic cleavage gives the expected Me₂HC–O•, but this reacts with 13 to remove the α -hydrogen to give 14 and 2-propanol. The carbon radical (14) fragments to acetone and Me₂HC–O•.²⁴ Acyl peroxides such as the commonly used benzoyl peroxide 9, react to give phenacyl radicals (15) that decarboxylates under the reaction conditions to give an aryl radical (such as 16). Decomposition of alkyl radical from an alkyl acyl precursor [(RCO₂)₂] leads to an alkyl radical. Decarboxylation of primary alkyl acyl peroxides such as acetyl peroxide (17) is very facile, leading to 18 and the methyl radical •CH₃.²⁴ Decarboxylation of aryl acyl radicals is slower. If a peroxide decomposes, the oxygen radical remains in a "cage" for about 10⁻¹¹ s before diffusing away. It can recombine (dimerize) or react further (see below).



Azo compounds, characterized by a -N=N- bond, are free radical precursors that liberate stable nitrogen gas (N=N) upon decomposition. One of the most used azo compounds is *azobis*(isobutyronitrile) (AIBN, **19**), which decomposes much faster than dibenzoyl peroxide to give nitrogen and the cyano stabilized radical **20**.²⁵ Just as with carbanion and carbocation

^{24.} Reference 4, p 13.

 ⁽a) Yoshino, K.; Ohkatsu, J.; Tsuruta, T. Polym. J. 1977, 9, 275; (b) Hinz, J.; Oberlinner, A.; Rüchardt, C.Tetrahedron Lett. 1973, 1975.

intermediates, the presence of the conjugating π bond in C=N will delocalize the single electron of the radical via resonance, increasing the stability of that intermediate. Homolytic dissociation of symmetrical diazo compounds may be stepwise,²⁶ as in the decomposition of **21** to **22** and triphenylmethyl radical (**23**). Azo radical **22** loses nitrogen to form **23**.²⁷ The decomposition temperature for diazo compounds is dependent on the groups attached to the α -carbon.²⁸ AIBN, for example, undergoes homolytic cleavage at ~ 67°C,²⁸ whereas MeN=NMe decomposes at about 275°C and *azobis*(2,2-dimethylethane) (Me₃CN=NCMe₃) decomposes at 172°C.²⁸ The stability imparted by the electron-withdrawing cyano group leads to greater stability of the radical and more facile decomposition.

13.4. PHOTOCHEMICAL FORMATION OF RADICALS

The general principles of photochemistry were introduced in section 11.10.B. A molecule can absorb a photon of light and the resultant photoactivated species can, in the context of this chapter, undergo homolytic cleavage to form radicals. As discussed in Chapter 11, the energy required for bond cleavage can be provided by various wavelengths of light. An energy of 10 kcal mol⁻¹ (42 kJ mol⁻¹) corresponds to 3500 cm⁻¹, which is in the IR. Light of wavelength 2000 Å corresponds to 143 kcal mol⁻¹ (598 kJ mol⁻¹), and is at the lower end of the ultraviolet (UV) region. Light in the UV or visible region can excite molecules to higher electronic states. Wavelengths in the UV are usually expressed in nanometers (1 nm = 1 mµ = 1 x 10⁻⁷ cm) and a wavelength of 200-400 nm is used most often for inducing photolysis in the UV region²⁹ for common functional groups (sec. 11.10.B).

If a molecule were irradiated with a light source generating several intense wavelengths of light, it is possible for several different functional groups to absorb the light and react, including the product we are trying to synthesize. A convenient method for limiting the wavelength of light (and thereby the energy of irradiation) is to filter out higher energy wavelengths (and

^{26.} Dannenberg, J.J.; Rocklin, D. J. Org. Chem. 1982, 47, 4529.

^{27.} Newman Jr., R.C.; Lockyer Jr., G.D. J. Am. Chem Soc. 1983, 105, 3982.

^{28.} Reference 4, p 15.

^{29.} Johnson, E. in *The Physiology and Pathophysiology of the Skin, Vol.* 8 of *The Photobiology of the Skin:* Lasers and the Skin, Jarrett, A. (Ed.), Academic Press, **1984**, p 2401.

lower energy if necessary). The filter is imposed between the light source and the reactants. Sometimes this is simply the reaction vessel, made of Pyrex or quartz glass,^{30,31} but more often the filter material is attached to the light source.

When a molecule absorbs a photon of light, an electron is promoted from the bonding to an antibonding molecular orbital ($n \rightarrow \sigma^*$, $n \rightarrow \pi^*$, or $\pi \rightarrow \pi^*$) to generate the singly occupied molecular orbital (a **SOMO**) pertinent to radical reactions (sec. 11.10.B).³² If the excited state is expressed as AB*, there are several pathways available for dissipation of this energy as shown by Wayne (Figure 13.3).³³ The pathway that is pertinent to formation of radicals is dissociation of AB* to A• and B•:



Figure 13.3. Routes Available For Loss of Electronic Excitation.

Photochemical homolysis of the carbon-carbon bond of alkanes is difficult. The carbon-carbon bond of ethane has a bond strength of 83 kcal mol⁻¹ (347.4 kJ mol⁻¹), and it fragments to methyl radicals (•CH₃) only at temperatures approaching 600°C. Absorption of a photon of light is also difficult since alkanes absorb only in the "vacuum" UV (methane absorbs at 144 nm = 198.6 kcal mol⁻¹ = 831.4 kJ mol⁻¹).³⁴ Loss of molecular hydrogen (H₂) usually accompanies conversion of an alkane (**24**) to the alkyl radical (**25**).³⁵ If a long alkyl chain is present, loss of H• can occur at many points, leading to a large number of different radicals.

^{30.} Murov, S.L. Handbook of Photochemistry, Marcel-Dekker, New York, 1973, pp 107-108.

^{31.} Calvert, J.G.; Pitts Jr., J.N. Photochemistry, Wiley, New York, 1966, pp 474, 490-491.

^{32.} DePuy, C.H.; Chapman, O.L. *Molecular Reactions and Photochemistry*, Prentice-Hall, Englewood Cliffs, New Jersey, *1972*, p 6.

^{33.} Wayne, R.P. Principles and Applications of Photochemistry, Oxford University Press, Oxford, 1988, p 6.

^{34.} Reference 33, pp 47 and 51.

^{35.} Reference 33, p 51.

Alkenes show a $\pi \to \pi^*$ absorption for the π bond at ≈ 180 nm (158.9 kcal mol⁻¹, 665.1 kJ mol⁻¹).³⁵ Conjugated alkenes show a shift in absorption toward the visible spectrum (lower energy). Isomerization (of ethene to ethyne) and fragmentation are observed.³⁵ The vield of alkenyl radical decreases as the size of the alkyl portion of 1-alkenes increases.³⁶ Photolysis of a terminal alkene generates radical **26** in a typical photolysis reaction.

Carbonyl compounds show a symmetry forbidden $n \rightarrow \pi^*$ transition at ~290 nm (98.6 kcal mol⁻¹, 412.8 kJ mol⁻¹) for aliphatic aldehydes, and at ~280 nm (102.1 kcal mol⁻¹, 427.6 kJ mol⁻¹) for ketones. Conjugation to an aromatic ring (as in benzophenone) shifts the absorption to longer wavelength (~340 nm, 84.1 kcal mol⁻¹, 52.1 kJ mol⁻¹). Acid derivatives absorb at a shorter wavelength [<250 nm (114.4 kcal mol⁻¹, 478.9 kJ mol⁻¹) for acids, anhydrides, and so on, and <260 nm (110 kcal mol⁻¹, 460.5 kJ mol⁻¹) for amides].³⁷ The allowed transitions ($\pi \rightarrow \pi^*$ and $n \rightarrow \sigma^*$) absorb at shorter wavelengths [about 180 and 160 nm (158.9 and 178.8 kcal mol⁻¹, 665.2 and 748.5 kJ mol⁻¹)] for aldehydes.³⁷

There are two main dissociative fragmentations for carbonyls upon photolysis, **Norrish type I**, and **Norrish type II** fragmentations.³⁸ Norrish type I cleavage involves loss of carbon monoxide (CO) and generation of an alkyl radical. For acetone, absorption of a photon leads to cleavage to the methyl radical and the acyl radical (**18**). Subsequent fragmentation of **18** leads to another equivalent of methyl radical with concomitant loss of CO. Loss of CO is not always observed, particularly if coupling of the radicals gives a different product, and is a faster process. In a synthesis of the hamigerans, for example, Nicolaou and co-workers observed that irradiation of ketone **27** led to a 93% yield of a 1:3 mixture of **27**:**29**.³⁹ This photochemical epimerization likely proceeded by diradical **28**, the Norrish type I process.



- 36. Shimo, N.; Nakashima, N.; Ikeda, N.; Yoshihara, K. J. Photochem. 1986, 33, 279.
- 37. Reference 33, p 52.
- (a) Norrish, R.G.W.; Bamford, C.H. *Nature (London)* 1937, 140, 195; (b) *Idem Ibid.* 1936, 138, 1016; (c) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-66.
- 39. Nicolaou, K.C.; Gray, D.L.F.; Tae, J. J. Am. Chem. Soc. 2004, 126, 613.

The Norrish type II process is an intramolecular fission of the bond α - β to the carbonyl (as in the fragmentation of **30** to 2,3-dimethyl-2-butene and enol **31**). The enol tautomerizes to a carbonyl compound, here acetone.



Similarly, photolysis of 2-pentanone undergoes cleavage to ethene and **31**, likely via a six-center transition state such as **32**.⁴⁰ This reaction is analogous to a **McLafferty rearrangement**,⁴¹ which is observed in the mass spectrum of ketones having at least three saturated carbon atoms attached to the carbonyl unit. A synthetic example of a Norrish-type II process is the preparation of azepine-fused oxetanols from alkoxy-substituted maleimides by Booker-Milburn and co-workers.⁴² Irradiation of maleimide **33** led to **34** via a [5+2] cycloaddition.⁴³ Further irradiation of **34** under the reaction conditions led to diradical **35**, and a Norrish type II process gave diradical **36**. β -Fission with expulsion of acetone led to **37**, and tautomerization gave **38** in 31% yield. Note that a different pathway formed 47% of other products.



^{40.} Reference 33, p 53.

- 42. Booker-Milburn, K.I.; Baker, J.R.; Bruce, I. Org. Lett. 2004, 6, 1481.
- Booker-Milburn, K. I.; Anson, E. A.; Clissold, C.; Costin, N. J.; Dainty, R. F.; Murray, M.; Patel, D.; Sharpe, A. *Eur. J. Org. Chem.* 2001, 1473.

 ⁽a) McLafferty, F.W. Anal. Chem. 1959, 31, 82; (b) Kingston, D.G.I.; Bursey, J.T.; Bursey, M.M. Chem. Rev. 1974, 74, 215; (c) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-58; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 414-415.

The Norrish type I process is considered to be the mechanism by which radicals are formed. The regiochemical outcome of Norrish type I cleavage depends on the wavelength of light employed. Photolysis of 2-butanone at 313 nm (91.4 kcal mol⁻¹, 382.5 kJ mol⁻¹) gave a 40:1 mixture of **39** and ethyl radical (CH₃CH₂•). Irradiation at 253.7 nm (112.7 kcal mol⁻¹, 471.9 kJ mol⁻¹), however, gave a 2.4:1 mixture of methyl radical and acyl radical **18**.⁴⁴

Aldehydes show an elimination reaction (loss of carbon monoxide, CO) that is not possible with ketones. Butanal, for example, photodissociates to propane and carbon monoxide. Apart from the reaction shown for **34**, cyclic ketones such as cyclopentanone dissociate to a diradical (in this case **40**), which then reacts in any of several ways including elimination to ethene or **41** and coupling to cyclobutane. Formation of cyclobutane and ethene is accompanied by expulsion of CO prior to formation of the alkene or the cyclic alkane.⁴⁰ The Norrish reactions



can occur with the reaction of an alkane and an aromatic ketone such as benzophenone,⁴⁵ to give radicals **42** and $\mathbb{R}^{46,47}$ Benzophenone acts as a sensitizer in this reaction. As discussed in Section 11.10.B, a **sensitizer** (S*) is added to facilitate electron

transfer between two molecules.⁴⁸ The use of a sensitizer involves transfer of excitation energy from an electronically excited molecule (the sensitizer) to the ground state of another molecule, usually providing a triplet excited state.^{49,32,33}

Bimolecular halogens (Cl₂, Br₂, etc.) and alkyl halides also serve as a source of radicals. Gaseous molecular iodine (I₂) gave the radical (I•) upon photolysis at about 500 nm (57.2 kcal mol⁻¹, 239.4 kJ mol⁻¹).⁵⁰ Other halogens behave similarly, although they absorb at shorter wavelength. Alkyl halides cleave into alkyl radicals and halogen radicals upon absorption of light, presumably via a diradical cage species represented by **43**.⁵¹ Alkyl iodides appear to generate intermediates $R = X \xrightarrow{hv} [R \cdot X] \longrightarrow R \cdot + X \cdot 43$

49. Breslow, R. Chem. Soc. Rev. 1972, 1, 553.

51. Kropp, P.J. Acc. Chem. Res. 1984, 17, 131.

^{44.} Reference 33, pp 52-53.

^{45. (}a) Murai, H.; Jinguji, H.; Obi, K. J. Phys. Chem. 1978, 82, 38; (b) Wagner, P.J.; Truman, R.J.; Scaiano, J.C. J. Am. Chem. Soc. 1985, 107, 7093.

^{46.} Sonawane, H.R.; Nanjundiah, B..; Rajput, S.I.; Udaya Kumar, M. Tetrahedron Lett. 1986, 27, 6125.

^{47.} Reference 4, p 22.

^{48.} Eaton, D.F. Pure App. Chem. 1984, 56, 1191.

^{50.} Reference 4, p 19.

with significant ionic character, whereas alkyl bromide intermediates show much more radical character.

As discussed in Section 11.10.B, the efficiency of the photolysis is measured by the **quantum** yield (or **quantum efficiency**): the number of reacted or formed molecules per absorbed light quantum.⁵² Quantum yield is measured for formation of a product (Φ_{form}) as just defined. It can also be defined in terms of the number of molecules of starting material (SM), which disappear per quantum of light (Φ_{dis}):⁵³

$$\Phi_{\text{form}} = \frac{\text{No. of molecules of product formed}}{\text{No. of quanta absorbed}}$$

$$\Phi_{\text{dis}} = \frac{\text{No. of molecules of SM destroyed}}{\text{No. of quanta absorbed}}$$
13.1
13.2

13.5. REACTIONS OF FREE RADICALS

Davies and Parrott⁵⁴ discuss several types of reactions available to radicals once they have been generated. General aspects of radical chemistry have also been discussed.⁵⁵ This section will focus on the reaction types that are pertinent to synthetic applications or must be considered as competing processes in synthetic applications. It is noted that a chiral auxiliary has been developed for reactions involving hydroxyalkyl radicals.⁵⁶ Indeed, a body of work has appeared that shifts attention from chemoselectivity and regioselectivity, to control of stereochemistry in radical reactions.⁵⁷ Sibi and co-workers have reviewed enantioselective radical processes.⁵⁸

The reactivity of free radicals is linked to their stability. Reactivity is a function of spin density of the atom and the type of orbital occupied by the unpaired electrons. Increasing the number

of atoms in a radical generally decreases reactivity, making monatomic radicals such as Li• and F• very reactive. Conjugation decreases the spin density and therefore the reactivity. The resultant delocalization does not necessarily lead to a very stable radical.⁵⁹ Steric effects play a significant role in radical reactivity.



^{52.} Reference 4, p 20.

^{53.} Reference 32, p 76.

^{54.} Reference 3, pp 1-14.

^{55.} Alfasi, Z.B. General Aspects of the Chemistry of Radicals, John Wiley, Chichester, 1999.

^{56.} Garner, P.; Anderson, J.T.; Cox, P.B.; Klippenstein, S.J.; Leslie, R.; Scardovi, N. J. Org. Chem. 2002, 67, 6195.

 ⁽a) Renaud, P.; Gerster, M. Angew. Chem. Int. Ed. 1998, 37, 2563; (b) Smadja, W. Synlett 1994, 1; (c) Porter, N.A.; Giese, B.; Curran, D.P. Acc. Chem. Res. 1991, 24, 296; (d) Giese, B. Angew. Chem. Int. Ed. 1989, 28, 969.

^{58.} Sibi, M.P.; Manyem, S.; Zimmerman, J. Chem. Rev. 2003, 103, 3263.

^{59.} Reference 4, p 147.

"If the bulkiness of the surrounding substituents exceeds about 12-fold that of the central atom containing a radical site", the radical is unreactive and fails to react at all in many cases.⁵⁹ Triphenylsilyl radical (**44**) is very reactive, but perchlorobenzyl radical (**45**) is not.

The reactivity of radicals can be explained by molecular orbital theory, in a manner similar to that used for Diels-Alder reactions (secs. 11.2-11.4). Lázar et al. listed four rules that define an allowed reaction of a radical:⁶⁰

- 1. The HOMO and LUMO of the reactant are decisive for the reaction course. At the mutual approach of reactants, there occurs the stabilization interaction between HOMO and LUMO. This interaction may be understood as a partial flow of electrons from the filled molecular orbitals to the empty ones.
- **2.** The frontier orbitals should be of a proper symmetry to achieve the most efficient overlap. Only molecular orbitals of the same symmetry can be mixed.
- **3.** The energy difference between HOMO and LUMO should be low (6 eV maximum). Presuming that point (2) is not fulfilled for some reason, the role of the frontier orbitals may be shifted to other orbitals of proper symmetry having the required energy difference.
- 4. If both orbitals are bonding, the HOMO should correspond to decaying bonds and LUMO to forming bonds. The opposite is true for an antibonding orbital.



Figure 13.4. The Interaction of a SOMO of a Radical With the Frontier Orbitals of a Molecule: (A) Somo-Lumo Interaction, (B) Somo-Homo Interaction.⁶¹ [Reprinted with permission from Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley, London, *1976*, pp. 183. Copyright © *1976* by John Wiley and Sons, Inc.]

A **SOMO**, defined above and in Section 11.10.B, can react with either a HOMO or a LUMO of another molecule as shown in Figure 13.4.⁶¹ The SOMO-LUMO interaction (as in Figure 13.4) occurs with nucleophilic radicals (high energy SOMO) that react best with molecules possessing a low energy LUMO (electron-deficient alkenes, sec. 11.2, Table 11.1). Conversely, the SOMO-HOMO interaction dominates with electrophilic radicals (low-energy SOMO), which react best with molecules possessing a high-energy HOMO (electron rich alkenes). Radical **46** has unpaired electrons closer to the carbonyl and is expected to have a low-energy

^{60.} Reference 4, p 137.

^{61.} Fleming, I. Frontier Orbitals and Organic Chemical Reactions, Wiley, London, 1976, p 183.


SOMO, making it an electrophilic radical. Radical **47** possesses a radical center closer to the oxygen, has a high energy SOMO, and is a nucleophilic radical. Radical **46** is expected to react best with electron-rich alkenes such as vinyl ethers, and **47** with

electron deficient alkenes such as acrylates. The SOMO energy is taken to be the ionization potential (IP, see sec. 11.2) of the radical.

Table 13.1⁶² shows the SOMO energies for several free radicals. In Section 11.2, Table 11.1, the LUMO and HOMO energies of a variety of alkenes were listed. The LUMO of methyl acrylate is 0 eV and the HOMO is -10.72 eV. The LUMO of methyl vinyl ether is +2.0 eV and the HOMO is -9.05 eV. Comparison of the SOMO energy of methyl radical (H₃C• in Table 13.1, -9.8 eV) and the acetate radical (HO₂CCH₂• in Table 13.1, -10.9 eV) shows that both reactions are SOMO_{radical}-HOMO_{alkene} controlled. The methyl radical will react somewhat faster with methyl vinyl ether than with methyl acrylate, but acetate radical will react significantly faster than the radical with the higher energy SOMO. The greater the SOMO_{radical}-HOMO_{alkene} (or SOMO_{radical}-LUMO_{alkene}) energy difference, the faster the reaction (see Figure 13.5).

 Table 13.1
 The SOMO Energies (IP) for Common Radical Types

<u>Radical (R•)</u>	SOMO Energy (eV)	<u>Radical (R•)</u>	SOMO Energy (eV)	<u>Radical (R•)</u>	SOMO Energy (eV)		
Me ₃ C•	-6.8	$\mathrm{C_{10}H_{23}CH_{2}\bullet}$	-8.7	t-BuO−O•	-11.5		
\frown	-7.8	∕_>•	-9.2	$HO_2CCH_2 \bullet$	-10.9		
$C_5H_{11}CH(Me)$ •	-7.8	$\overline{H_3}C\bullet$	-9.8	Cl•	-13.0		
Et ₃ Si•	-7.0	H•	-13.6	Br∙	-11.8		
Me ₃ Si•	-7.0	t-BuO•	-12.0	Cl ₃ C∙	-8.8		
[Reprinted with permission from Fleming, I. Frontier Orbitals and Organic Chemical Reactions, Wiley, London, 1976, pp. 186. Copyright © 1976 by John Wiley and Sons. Inc.]							



Figure 13.5. The SOMO-HOMO Interactions For Methyl And Acetate Radicals With Methyl Acrylate and Methyl Vinyl Ether.

^{62.} Reference 61, p 186.

There are several major reaction types available to radicals: coupling, addition, substitution, fragmentation, rearrangement and oxidation. However, there are three main reaction types: coupling, addition and atom transfer. The frontier molecular orbital treatment shown here for addition to alkenes can, with modification, be used to predict reactivity in virtually all radical reactions. The following sections will describe the various radical reaction types.



One reason to expect that the chloride shown below will lead to a "non-reactive" radical is that the unpaired electron is delocalized onto both fluorenyl rings as well as onto the phenyl ring.



Spin density maps portray the number of unpaired electrons on an electron density surface. By convention, "blue" regions indicate an excess of unpaired electrons. Compare the map for this radical with maps for cyclopentyl and fluorenyl radicals. Which shows least delocalization and which shows greatest delocalization? Which would you expect to be least reactive and which most reactive?

A second reason is that the sp³ carbon in the radical precursor is likely to be very crowded. *Click* on > and the select *Continue*. Build the precursor chloride and obtain its geometry. Repeat the process for the chloride precursors to the cyclopentyl and fluorenyl radicals. Is the double bond in the bis (fluorenyl) radical unusually long (a typical C=C length is 1.32Å) or is it twisted or puckered or both?

13.5.A. Coupling

Two radicals can combine to form a new carbon bond, as in the coupling of two ethyl radicals (CH_3CH_2) to give butane. When one of the radical moieties possesses a β -hydrogen (or a β -leaving group), disproportionation can occur to form an alkene and an alkane. Ethyl radicals, for example, react to give ethane and ethene by disproportionation. Disproportionation can compete with coupling, but depends on the method used to generate the radical. Resonance stabilized radicals are less prone to disproportionation. In a solvent, a radical is more likely to encounter a solvent molecule or a substrate rather than disproportionate, although coupling is sometimes competitive.

If the radical is particularly stable (such as diphenylmethyl radical, **48**), coupling with a second radical molecule (to give **49**) is preferred to disproportionation, but this is not always the case. Triphenylmethyl radical (**4**), for example, possesses significant steric encumbrance at the radical

carbon such that attack at a phenyl ring is preferred (to give 50 rather than Ph_3CCPh_3).⁶³



13.5.B. Addition Reactions



 $\begin{array}{c} & & \\ & &$ -- in the presence of the alkene, a chain reaction is possible in

which the newly formed radical adds to unreacted alkene to generate another radical. An example is the radical polymerization of an alkene, as shown in Figure 13.6 (cationic polymerization tends to be more efficient in many cases and may be accomplished under milder conditions).



Figure 13.6. Chain Radical Addition Reactions.

An **initiation step** generates the radical, which in this case involves fragmentation of an alkyl peroxide to give RO... This radical adds to the alkene to give a new reactive species (52). Addition of a second molecule of alkene generates 53, and sequential addition to n molecules of alkenes generates 54. These are called chain propagation steps, in which each step

^{63.} Lankamp, H.; Nauta, W.T.; MacLean, C. Tetrahedron Lett. 1968, 249.

generates a reactive radical intermediate. If the radicals undergo coupling (several examples are shown, including formation of ROOR and **55**, as well as coupling to give **56**) the chain process stops since no radical is available to continue the process. This coupling is called a **chain termination** step because the product is *not* a radical. A new initiation step must occur to begin the chain process again. If a compound is added that will readily transfer a hydrogen atom, or another atom, to the radical this may stop the chain process in a controlled manner. Such a compound is called a hydrogen-transfer agent, or a radical quenching agent. Tributyltin hydride is an excellent hydrogen transfer agent in such reactions (see secs. 13.5.D, 4.9.H).

If the product radicals are stable, and/or if the stoichiometry of the reagents is controlled, a single product can be obtained in high yield. An example is the free radical addition of carbon tetrachloride (CCl₄) to styrene, which gives the benzylic radical **57** as an intermediate. Subsequent addition of **57** to styrene gives **59**. Addition of the benzyl radical to styrene (to produce another benzylic radical) is faster than chlorination⁶⁴ with a chlorine atom from carbon tetrachloride (which would give **58**), so polystyrene is the final product. When 1-octene reacted with CCl₄, however, the alkyl radical (**60**) was produced and coupling with a chlorine atom to give **62** was favored over addition to 1-octene (to give **61**, which was not observed). In fact, this reaction gave an 85% yield of **62**.⁶⁵





If a radical is generated in a substrate that also has a π bond in the molecule, intramolecular cyclization can occur (as in $63 \rightarrow 64$). The highly reactive radical center is positioned to react with the π bond of the alkene, as shown, and the product (64) can be trapped to give

the final product. Radical cyclization reactions will be discussed in Section 13.7.

^{64. (}a) Gregg, R.A.; Mayo, F.R. J. Am. Chem. Soc. 1948, 70, 2373; (b) Mayo, F.R. Ibid. 1948, 70, 3689.

^{65.} Kharasch, M.S.; Jensen, E.V.; Urry, W.H. J. Am. Chem. Soc. 1947, 69, 1100.

13.5.C. Substitution Reactions

A classical radical substitution reaction forms alkyl halides from the reaction of a diatomic halogen with a hydrocarbon such as toluene. Initiation of the reaction of bromine and toluene begins with photolytic cleavage of bromine, to give bromine radicals (Br₂ + hv \rightarrow 2 Br•). Diatomic bromine can also be converted to Br• by adding a peroxide or another radical initiator. Bromine radical abstracts a hydrogen atom from the α -carbon of toluene to give a resonance delocalized benzylic radical (65) and HBr. The benzylic radical abstracts a bromine atom from a second molecule of diatomic bromine to give benzyl bromide and Br•, the radical carrier in a chain propagation step.⁶⁶ This reaction can be applied to simple alkanes, if a relatively stable tertiary radical can be produced. The relative order of hydrogen abstraction has been shown to be⁶⁷

 $CH_3-H < CH_3CH_2-H < CH_3CH_2CH_2-H < Me_2CHCH_2-H < Me_2CH-H < Me_3C-H$

$$Br_{2} \xrightarrow{hv} 2 Br^{\bullet}$$

$$PhCH_{2}-H \xrightarrow{Br^{\bullet}} HBr + \left[\swarrow -\dot{C}H_{2} \leftrightarrow \swarrow -\dot{C}H_{2} \leftrightarrow \checkmark -\dot{C}H_{2} \leftrightarrow \checkmark -\dot{C}H_{2} \leftrightarrow \checkmark -\dot{C}H_{2} \leftrightarrow \land -\dot{C}H_{2} \leftrightarrow -\dot{$$

There is a great preference for forming tertiary radicals upon reaction of a hydrocarbon with bromine (via hydrogen atom abstraction by Br•). The relative rates for hydrogen atom abstraction by a bromine radical are 1 for primary hydrogen, 82 for secondary hydrogen and 1640 for a tertiary hydrogen, which means that a tertiary hydrogen will be abstracted to form the corresponding radical 1640 times faster than that for a primary hydrogen. When the radical reacts with more bromine to give the alkyl bromide, this selectivity leads to good vields of the tertiary bromide with smaller or trace amounts of isomeric bromides. This selectivity is not shared with the analogous chlorination reaction, however. For chlorination reactions, the relative rate of hydrogen atom abstraction is 1 for primary, 3.9 for secondary, and only 5.2 for tertiary, which means that a tertiary hydrogen atom is removed only 5.2 times faster than a primary, so there is much less selectivity. Halogen radicals will abstract all hydrogen atoms in the molecule, and when the rate of abstraction is close for different hydrogen atoms, as with the chlorine radical, the resulting carbon radicals react to give close to a statistical distribution of the corresponding isomeric chloride products. The significant difference in the rate of hydrogen atom abstraction by the bromine radical leads to good selectivity. The difference in selectivity between chloride and bromide radicals can also be explained by molecular orbital

^{66. (}a) Reference 3, p 7; (b) Kochi, J.K.; Buchanan, D. J. Am. Chem. Soc. 1965, 87, 853.

^{67.} Fukui, K.; Kato, H.; Yonezawa, T. Bull. Chem. Soc. Jpn. 1962, 35, 1475.

theory. A tertiary hydrogen (as in 2-methylpropane, HOMO = -10.4 eV)⁶⁸ is selectively removed by a bromine radical (SOMO = -11.8 eV, $\Delta E = 1.4 \text{ eV}$), but removal of this hydrogen by a chlorine radical (SOMO = -13.0 eV, $\Delta E = 3.4 \text{ eV}$) is less selective than with secondary and primary hydrogens. In other words, the difference in energy for removal of a tertiary versus a secondary hydrogen is greater in reactions with bromine radicals than with chlorine radicals. The bromine reactions are therefore more selective for removal of tertiary hydrogens. Ingold



and Roberts discussed free radical substitution reactions in great detail.⁶⁹ It is important to note that free radical substitution of hydrogen by bromine is accomplished with *N*-bromosuccinimide (NBS), and that by chlorine with

N-chlorosuccinimide (NCS) if the alkane substrate contains an allylic or benzylic hydrogen (sec. 2.8.B). An example is the conversion of 1-phenylbutane (**66**) to 1-bromo-1-phenylbutane (**67**).

13.5.D. Reduction

When a radical is generated in the presence of a hydrogen transfer agent, it is possible to reduce various functional groups. Since an X group is replaced with H, this is a form of

the substitution reaction described in Section 13.5.C, but it is separated into a different section because of it synthetic importance and because it is formally a reduction. The best example may be the one presented in Section 4.9.H in



which an alkyl halide is reduced by treatment with tributyltin hydride, illustrated here by the reduction of iodide **68** in the presence of AIBN and Bu₃SnH to give a 98% yield of **69** in an example taken from Davis and co-worker's⁷⁰ synthesis of pyrrolidine (–)-197B. AIBN (**19**) is a radical initiator, and leads to loss of iodide to give the radical. The intermediate radical reacted with Bu₃SnH via hydrogen transfer to give **69** and Bu₃Sn•, which generated Bu₃SnI. This reaction is a very effective method for the controlled reduction of halides.



A very useful radical-based reaction has been developed that can be applied to alcohols. As seen in chapter 4, conversion of an alcohol to a thionocarbonate followed by treatment with tributyltin hydride under radical conditions gives cleavage to the C–O bond to give the reduction product. This transformation called the **Barton deoxygenation** (**Barton-McCombie**

^{68.} Fukui, K.; Kato, H.; Yonezawa, T. Bull. Chem. Soc. Jpn. 1960, 33, 1197.

^{69.} Ingold, K.U.; Roberts, B.P. Free Radical Substitution Reactions, Wiley, New York, 1971.

^{70.} Davis, F.A.; Song, M.; Augustine, A. J. Org. Chem. 2006, 71, 2779.

reaction).⁷¹ In a synthesis of crispatenine by Commeiras, Parrain and co-workers,⁷² treatment of **70** with sodium hydride and carbon disulfide, followed by iodomethane, gave xanthate **71**, and subsequent reduction with tributyltin hydride and AIBN gave a 90% yield of **72**.

13.5.E. Fragmentation

Aradical can fragment to form a new radical and a neutral molecule. Typically, the neutral molecule is an alkene, making the overall process a simple elimination.⁷³ Addition of trichloromethyl radical (Cl₃C•), generated by thermolysis of the acyl peroxide **73** to 2,3-dimethyl-2-butene, gave **74**. Abstraction of a hydrogen atom⁷⁴ by •CCl₃ gave trichloromethane and **76**. Transfer of a hydrogen atom to **74** (from solvent, the alkane, or a hydrogen atom), however, led to **75**.

$$Cl_{3C} \xrightarrow{O} CCl_{3} \xrightarrow{CCl_{4}} CCl_{3} \xrightarrow{CCl_{3}} Ccl_{3} \xrightarrow{CCl_{3}} Cl_{3C} \xrightarrow{H^{*}} Cl_{3C} \xrightarrow{H^{*}} Cl_{3C} \xrightarrow{75} Cl_{3C} \xrightarrow{75} Cl_{3C} \xrightarrow{75} Cl_{3C} \xrightarrow{76} Cl_{3C}$$

Both processes occurred in this reaction, and are typical of radical additions. Alkoxy radicals such as **78** (formed via loss of a chlorine atom from hypochlorite **77**) often lose a hydrogen atom (to give 2-butanone when R = H) or an alkyl radical (to give **79** when R = Me) via cleavage of the bond β to the radical center.⁷⁵ Thermolysis of hypochlorite **80**, for example, gave acetone and chloroethane via coupling of the intermediate ethyl radical with alkoxy radical **81**.⁷⁶ Hypochlorites are excellent sources of alkoxy radicals, and can be used to initiate other radical reactions.



 ⁽a) Barton, D.H.R.; McCombie, S.W. J. Chem. Soc. Perkin Trans. 1 1975, 1574; (b) Lopez, R.M.; Hays, D.S.; Fu, G.C. J. Am. Chem. Soc. 1997, 119, 6949. Phenyl thionocarbonates were first used by (c) Robins, M.J.; Wilson, J.S.; Hansske, F. J. Am. Chem. Soc. 1983, 105, 4059; (d) Robins, M.J.; Wilson, J.S. J. Am. Chem. Soc. 1981, 103, 932; See (e) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-6; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 68-69.

74. Loken, H.Y.; Lawler, R.G.; Ward, H.R. J. Org. Chem. 1973, 38, 106.

76. Chattaway, F.D.; Baekeberg, O.G. J. Chem. Soc. 1923, 123, 2999.

^{72.} Bourdron, J.; Commeiras, L.; Audran, G.; Vanthuyne, N.; Hubaud, J.C.; Parrain, J.-L. J. Org. Chem. 2007, 72, 3770.

^{73.} Wilt, J.W., Chapter eight in Free Radicals, Vol 1, Kochi, J.K. (Ed.), Wiley, New York, 1973, p 333.

^{75.} Reference 3, p 9.



13.5.F. Rearrangement and Hydrogen Abstraction

There are a few rearrangement processes of free radicals.^{77,64} When chlorine, phenyl, acetoxy, and acyl groups are in the β -position with respect to the radical center, 1,2-shifts have been observed. An example is the rearrangement of **82** to **84** via **83**.⁷⁸

$$\begin{bmatrix} X \longrightarrow \stackrel{Ph}{\longleftarrow} O \bullet \\ Ph \end{bmatrix} \longrightarrow \begin{bmatrix} X \longrightarrow \stackrel{Ph}{\longleftarrow} O \bullet \\ 82 \end{bmatrix} \longrightarrow \begin{bmatrix} X \longrightarrow \stackrel{Ph}{\longleftarrow} O \bullet \\ 83 \end{bmatrix} \longrightarrow \begin{bmatrix} Y \longrightarrow \stackrel{Ph}{\longleftarrow} O \bullet \\ X \longrightarrow O \bullet \\ 84 \end{bmatrix}$$

Skeletal reorganization occurs in radical intermediates primarily via hydrogen atom shifts observed that are probably hydrogen abstraction reactions. An example is the **Barton** reaction,⁷⁹ in which an alkoxy radical (86), generated from the hypochlorite (85), abstracts a hydrogen atom via a six-center transition state to give 87. Subsequently, 87 abstracts a chlorine atom from 85 to give 88 and regenerate reactive radical 87.⁸⁰ In a synthetic example, Barton and co-workers converted 3 β -acetoxy-5 α -pregnan-20 β -ol (89) to the nitrite derivative (90) via reaction with nitrosyl chloride (NOCl).^{79a} Photochemical cleavage (mercury lamp and a Pyrex filter) of 90 generated alkoxy radical 91, which abstracted the hydrogen atom from the neighboring methyl that was properly positioned for reaction via a six-center transition state by virtue of the rigid steroidal structure. The newly formed radical (92) was trapped by the nitrosyl radical to give 93 and treatment with water gave the oxime (94) in 34% yield. Hydrolysis with dilute acid gave lactol 95. The net result is an oxidation (-CH₃ \rightarrow -CHO; sec. 3.8).



^{77. (}a) Walling, C. Free Radical Rearrangements in Molecular Rearrangements, Vol 1, chapter 7, de Mayo, P. (Ed.), Wiley, New York, **1963**, p 407; (b) Freidlina, R.Kh. Adv. Free Radical Chem. **1965**, 1, 211.

^{78.} Kharasch, M.S.; Poshkus, A.C.; Fono, A.; Nudenberg, W. J. Org. Chem. 1951, 16, 1458.

 ⁽a) Barton, D.H.R.; Beaton, J.M.; Geller, L.E.; Pechet, M.M. J. Am. Chem. Soc. 1960, 82, 2640; (b) Idem Ibid. 1961, 83, 4076; (c) Barton, D.H.R. Pure Appl. Chem. 1968, 16, 1; (d) Hesse, R.H. Adv. Free Radical Chem. 1969, 3, 83; (e) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-6; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 66-67.

^{80.} Walling, C.; Padwa, A. J. Am. Chem. Soc. 1963, 85, 1593, 1597.



The reaction is not restricted to steroids, but simply requires that the abstracted hydrogen atom is positioned close enough to react with the alkoxy radical. Reaction of alcohol **96** with bromine and mercuric bromide gave the corresponding hypobromite (-OH \rightarrow -OBr). Subsequent photolysis gave a 43% yield of **97**.^{81a,b} Oxidation with chromium trioxide in acetic acid gave the lactone (**98**), which was used by Magnus in a synthesis of grandisol.^{81d} Gibson and Erman used similar intermediates and methodology for the synthesis of cis-bergamotenes.^{81c}

$$Me \xrightarrow{Me}_{96} OH_{Me} \xrightarrow{1. HgO, Br_2, CCl_4, 0^{\circ}C}_{2. hv (tungsten lamp), 0^{\circ}C} Me \xrightarrow{O}_{97} Me \xrightarrow{AcOH, CrO_3}_{80^{\circ}C} Me \xrightarrow{O}_{98} Me$$

Note that there are potential side reactions. Once the oxygen radical is generated, the hydrogen can be abstracted via a four-center transition state if the six-center transition state is not readily accessible. A Barton-like reaction involved photolysis of **99** to give the oxygen radical **100**.⁸² Removal of H_a in **100** via a five-center transition state (•O–C–C–C–H) gave the corresponding carbon radical (**101**), which gave two products via either cyclization in the presence of the alkene and trapping by NO (to give **102**, 25% yield) or by direct trapping with NO to give **103** (14% yield).



 ⁽a) Bosworth, N.; Magnus, P.D. J. Chem. Soc. Perkin Trans. 1 1972, 943; (b) Hortmann, A.G.; Youngstrom, R.E. J. Org. Chem. 1969, 34, 3392; (c) Gibson, T.W.; Erman, W.F. J. Am. Chem. Soc. 1969, 91, 4771; (d) Hobbs, P.D.; Magnus, P.D. J. Am. Chem. Soc. 1976, 98, 4594.

82. Čeković, Ž.; Ilijev, D. Tetrahedron Lett. 1988, 29, 1441.

13.6. INTERMOLECULAR RADICAL REACTIONS

In 1849 Kolbe found that electrolysis of potassium acetate generated carbon dioxide (CO₂) and ethane, presumably via acetoxy radical **104** that lost carbon dioxide to give the methyl radical (•CH₃).⁸³ The methyl radical (•CH₃) coupled with another methyl radical to give ethane. The reaction works very well with long, straight chain alkanoic acids. This reaction is known as the **Kolbe electrolytic synthesis**^{83,84} and it was used to convert hexadecanoic acid to *n*-triacontane (*n*-C₃₀H₆₂) in 88% yield.⁸⁵ Kolbe electrosynthesis has been used to prepare rigid, rod-shaped hydrocarbons based on oligo-bicyclo[2.2.2]octane derivatives.⁸⁶ Much larger and more complex molecules can be synthesized by this method. Stork used the Kolbe electrosynthesis use to dimerize **105** to **106** (in 40% yield) in a synthesis of α -onocerin.⁸⁷ As illustrated by the synthesis of **106**, the reaction is very efficient when two identical acids are coupled together.



The Kolbe synthesis of two different acids (RCOOH + R'COOH) generally leads to a mixture of products arising from statistical coupling (R-R, R-R', R'-R'). Using an excess of one acid can lead to the desired mixed-coupling product (R-R'), as in the reaction of **107** with an excess of heptanoic acid to give **108** in 80% yield.⁸⁸ There are several variations.⁸⁸

$$n - C_8 H_{17} \underbrace{(CH_2)_7 - CO_2^-}_{107} + \underbrace{Me^{-(CH_2)_5}}_{excess} \underbrace{e^-}_{CO_2 H} \underbrace{n - C_8 H_{17}}_{108} \underbrace{(CH_2)_7 - (CH_2)_5}_{108}$$

Aldehydes can also be a source of radicals via reaction with transition metal salts such as Mn(III) acetate. Aldehyde-based radical addition to alkenes generates ketones such as **113**

- 87. Stork, G.; Meisels, A.; Davies, J.E. J. Am. Chem. Soc. 1963, 85, 3419.
- (a) Seidel, W.; Knolle, J.; Schäfer, H.J. Chem. Ber. 1977, 110, 3544; also see (b) Knolle, J.; Schäfer, H.J. Angew. Chem. Int. Ed. 1975, 14, 758; (c) Klünenberg, H.; Schäfer, H.J. Ibid. 1978, 17, 47.

^{83.} Kolbe, H. Annalen 1849, 69, 257.

 ⁽a) Crum Brown, A.; Walker, J. Annalen 1891, 261, 107; (b) Lindsey, A.S.; Jeskey, H. Chem. Rev. 1957, 57, 583; (c) Vijh, A.K.; Conway, B.E. Ibid. 1967, 67, 623; (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-53; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 372-373.

^{85.} Petersen, J.B. Z. Electrochem. 1906, 12, 141.

^{86.} Nuding, G.; Vögtle, F.; Danielmeier, K.; Steckhan, E. Synthesis 1996, 71.

in good yield.⁸⁹ An acyl radical is initially generated via reaction with the transition metal [Mn(III) and Fe(II) are the most common].⁹⁰ Reaction of butanal and 1-heptene in the presence of manganese acetate [Mn(OAc)₃] began with addition of the acyl radical (**109**) to both carbons of the π bond, giving regioisomers **110** (48% yield) and **111** (3% yield) as well as a 27% yield of **113** and a 22% yield of **114**. Removal of the hydrogen atom α to the carbonyl led to **112**, and addition to the alkene gave **113**.⁹¹ This reaction also occurs with ketones, but usually requires catalysis (with di-*tert*-butyl peroxide, for example).⁹² A simple application is seen in the coupling reaction of cyclopentanone with 1-decene to give 2-decylcyclopentanone in 71% yield.^{92b}



Giese describes many synthetic applications of radical coupling with alkenes.^{6,93} Reactions with simple alkenes are not very efficient, but reactions with alkenes bearing an electron-withdrawing group are usually quite facile. Perhaps the most common method for generating the radicals for reaction with alkenes is to heat an alkyl halide with AIBN (**19**), in the presence of tri-*n*-butyltin hydride (*n*-Bu₃Sn–H). In a typical reaction, AIBN is thermally decomposed (refluxing benzene) or decomposed by exposure to light, and the resulting radical intermediate reacts with iodocyclohexane to give **115**. This radical reacts with ethyl acrylate to give **116**. Tributyltin hydride is an efficient intermolecular hydrogen donor, reacting with **116** to form the product (**117**), and generate a chain-carrying radical Bu₃Sn•, which can react with additional halide to produce **115**. Giese and Gerth used this technique to couple **118** with methyl methacrylate, giving **119** in 70% yield.⁹⁴ Removal of the benzylidene acetal (sec. 7.3.B.i) by hydrogenation and subsequent lactonization gave malyngolide (**120**).⁹⁵ Table 13.2⁹⁵ shows the

- Nikishin, G.I.; Vinogradov, M.G.; Verenchikov, S.P.; Kostyukov, I.N.; Kereselidze, R.V. J. Org. Chem. USSR 1972, 8, 539 (Engl. p 544).
- (a) Nikishin, G.I.; Somov, G.V.; Petrov, A.D. Dokl. Akad. Nauk. 1961, 136, 1099; (b) Idem Izvest. Akad. Nauk. 1961, 2065 (Engl. p 1924); (c) Glukhovtsev, V.G.; Spektor, S.S.; Golubev, I.N.; Nikishin, G.I. J. Org. Chem. USSR 1973, 9, 316 (Engl. p 317).
- 93. (a) Giese, B. Angew. Chem. Int. Ed. 1983, 22, 753; (b) Idem Ibid. 1985, 24, 553.
- 94. Gerth, D.B.; Giese, B. J. Org. Chem. 1986, 51, 3726.
- 95. Reference 6, p 58.

^{89.} Reference 3, p 69.

^{90. (}a) Sosnovsky, G. Free Radical Reactions in Preparative Organic Chemistry, MacMillan, New York, 1964;
(b) inogradov, M.G.; Nikishin, G.I. Usp. Khim. 1971, 40, 1960; (c) Nikishin, G.I.; Vinogradov, M.G.; Il'ina, G.P. Synthesis 1972, 376.

radical coupling of representative alkyl halides and selected alkenes (to give **121**), under both photochemical and thermal conditions.



 Table 13.2
 Intermolecular Radical Coupling of Alkyl Halides and Alkenes

		- (8) (2)	% 121				% 121
Alkyl Halide	Alkene	hv	A (AIBN)	Alkyl Halide	Alkene	hy	A (AIBN)
n-C6H13I	CH2=CHCN	80		c-C6H111	Methyl vinyl ketone	85	
c-C6H11I	00070-00000000	95			Acrolein		90
t-C4HoI		87	98	1	Ethyl acrylate	85	
n-C6H13Br			68	1	Styrene	83	
c-C6H11Br			80	1	1,1-Dichloroethene	87	
t-C4H9Br		62		1	(E)-Dicyanoethene		72
				1	(E)-1-Cyano-1-propene	86	

A problem with radical coupling in the presence of a hydrogen donating species such as tin hydride is competing hydrogen transfer to directly reduce the alkyl halide (-CH₂I \rightarrow -CH₂H), as described in Section 13.5.D. If the initially formed radical is long lived and/or if the radical coupling reaction is slow, that radical can be reduced by hydrogen abstraction from the tin hydride. In some cases, the reduction process can be the major reaction, but about 20-25% yields are typical. α -Halo esters add to alkenes to form either lactones or substituted ester derivatives.^{96,97}

An alternative route has been used for radical coupling, involving alkyl halides and allyl tin derivatives (such as allyltributyltin, *n*-Bu₃SnCH₂CH=CH₂).^{98,101} Migata⁹⁹ and Peryne,¹⁰⁰

^{96.} Kharasch, M.S.; Skell, P.S.; Fisher, P. J. Am. Chem. Soc. 1948, 70, 1055.

^{97. (}a) Reference 11, p 501; (b) Giese, B.; Horler, H.; Leising, M. Chem. Ber. 1986, 119, 444.

^{98.} Keck, G.E.; Yates, J.B. J. Am. Chem. Soc. 1982, 104, 5829.

^{99. (}a) Kosugi, M.; Kurino, K.; Takayama, K.; Migata, T. J. Organomet. Chem. 1973, 56, C11; (b) Migata, T.; Nagai, K.; Kosugi, M. Bull. Chem. Soc. Jpn. 1983, 56, 2480.

^{100.(}a) Grignon, J.; Pereyne, M. J. Organomet. Chem. 1973, 61, C33; (b) Grignon, J.; Servens, C.; Pereyre, M. Ibid. 1975, 96, 225.

introduced allyltin compounds used in this context, but Keck and co-workers contributed significantly to the synthetic development of these reagents.^{101,98} Allyl tin compounds react with alkyl halides to give the corresponding coupling product (see sec. 12.9.A). An electron-withdrawing substituent at C2 of the allyl stannane increased the reactivity, illustrated by the coupling of bromoadamantane (**122**) and **123** to give **124** in 70% yield.¹⁰² It is not usually possible to use allyl stannanes bearing substituents at C1 or C3,¹⁰³ but there are exceptions.¹⁰⁴



When there is a substituent at the C3 position, addition of the radical is slow. When C1 is substituted the stannane can rearrange, which can be competitive with addition.¹⁰⁵ This latter problem was solved, at least for prenylation, by the use of an allyl sulfide precursor such as **125**. Keck and Byers showed that **126** reacted with **125** in the presence of tributyltin dimer (Bu₃Sn-SnBu₃) to give **127** in 76% yield.¹⁰⁶ Photolysis of tributyltin dimer generates two equivalents of Bu₃Sn•, which initiates the reaction. Good diastereoselectivity may be achieved in radical addition reactions. When **128** was treated with *tert*-butyl iodide, Bu₃SnH and Sc(OTf)₃, a 58% yield of **129** was obtained as a 1:99 anti/syn mixture.¹⁰⁷



When heteroatom containing substrates react with peroxides or other radical initiators, hydrogen atom transfer can occur as in the transfer of hydrogen from an acetal to the radical to give an alkane and the α -alkoxy radical **130**. The presence of the heteroatom α to the carbon

- 103. Reference 11, p 491.
- 104. Fliri, H.; Mak, C.-P. J. Org. Chem. 1985, 50, 3438.
- 105. (a) Keck, G.E.; Yates, J.B. J. Organomet. Chem. 1983, 248, C21; (b) Baldwin, J.E.; Adlington, R.M.; Basak, A. J. Chem. Soc. Chem. Commun. 1984, 1284.
- 106. Keck, G.E.; Byers, J.H. J. Org. Chem. 1985, 50, 5442.
- 107. (a) Hayen, A.; Koch, R.; Saak, W.; Haase, D.; Metzger, J.O. J. Am. Chem. Soc. 2000, 122, 12458. Also see (b) Hayen, A.; Koch, R.; Metzger, J.O. Angew. Chem. Int. Ed. 2000, 39, 2758.

^{101.} Keck, G.E.; Enholm, E.J.; Yates, J.B.; Wiley, M.R. Tetrahedron 1985, 41, 4079.

Baldwin, J.E.; Adlington, R.M.; Birch, D.J.; Crawford, J.A.; Sweeney, J.B. J. Chem. Soc. Chem. Commun. 1986, 1339.

bearing the radical center leads to enhanced stability. Such radicals add to alkenes, usually with anti-Markovnikov orientation, as in the radical induced addition of HBr to alkenes (sec. 2.10.A). The reaction usually involves slow addition of a large excess (5-10 equivalents) of the heteroatom containing substrate. Peroxides and peroxyesters are the usual radical initiators. The hydrogen atom transfer reaction is often very slow, and an excess of the hydrogen atom donor (the heteroatom substrate) and higher reaction temperatures are essential.¹⁰⁸ Curran showed several general examples of this type of reaction involving alcohols (to give **131**), esters (to give **132**), amines (to give **133**) or aldehydes (to give **134**).¹⁰⁹



Alkynes are generally less reactive than alkenes in radical coupling reactions since the LUMO of the alkyne is energetically higher than the LUMO of an alkene (sec. 11.2.A, Table 11.1). Formation of the requisite SOMO is therefore more difficult.¹¹⁰ The intermediate vinyl radical (**135**) undergoes coupling to give a mixture of cis and trans isomers, as shown but when R is bulky the cis compound (**136**) is favored via trans-attack. An example is formation of **115** from cyclohexyl mercuric acetate, which added to 1-phenylethyne to give a 70:30 mixture of **137/138** in 8% yield.¹¹⁰ Addition to methyl propiolate showed better reactivity, but poorer selectivity.¹¹⁰ As the size of R increases, syn approach of the hydrogen donor is increasingly hindered.¹¹⁰ Nonradical nucleophiles usually react faster with alkynes than with alkenes, however.¹¹¹



The disconnections that are pertinent to intermolecular radical coupling reactions include

$$\begin{bmatrix} R \\ R \\ R \\ R \\ R^{2} \end{bmatrix} \xrightarrow{CO_{2}H} R^{1} \xrightarrow{O} R^{1} \xrightarrow{O} R^{1} \xrightarrow{O} R^{1} \xrightarrow{O} R^{1} \xrightarrow{O} R^{-CHO^{+}} \xrightarrow{R^{1}} R \xrightarrow{X} \xrightarrow{O} R^{-X^{+}} \xrightarrow{Z}$$

- 109. Reference 11, p 498.
- 110. (a) Giese, B.; Lachhein, S. Angew. Chem. Int. Ed. 1982, 21, 768; (b) Giese, B.; Meixner, J. Ibid. 1979, 18, 154.
- 111. Dickstein, J.I.; Miller, G.I. in *The Chemistry of Carbon Carbon Triple Bonds, Vol. 2*, Patai, S. (Ed.), Wiley, New York, *1978*.

^{108.} Reference 11, p 497.

13.7. INTRAMOLECULAR RADICAL REACTIONS (RADICAL CYCLIZATION)

13.7.A. Carbocyclic Ring Systems

There are many examples of radical reactions that produce rings.^{11,112} The fundamentals of the reaction can be illustrated by the AIBN induced reaction of tributyltin hydride and 139 (X =I or Br), which generates radical 63. Once formed, at least three pathways are possible under these conditions.¹¹³ The first is **path** a, a 5-exo-trig-cyclization to give 64. Path b is a 6-endotrig-cyclization to give 115. These descriptors are based on **Baldwin's rules** (sec. 6.6.A) and both pathways are favored. The last pathway is the usual hydrogen-transfer process where tin hydride reacts with 63 to give 140 (path c), as discussed in Section 13.5.D. In general, the 5-exo-trig-pathway is lower in energy than **path** b and faster than **path** c, leading to 64 as the major product. This outcome is subject to steric effects or electronic effects that arise from interaction of substituents on the alkenyl moiety. At high concentrations (> 5 M), hydrogen transfer to give 140 usually predominates so radical cyclization reactions are typically done at low concentrations (< 0.05 M).¹¹ In cases where path c is faster than path a or b, photolysis in the presence of n-Bu₃Sn-Snn-Bu₃ and a halogen transfer agent such as an iodoalkane usually gives cyclized products such as 64 or 115 rather than 140 (see below). Dilauroyl peroxide has also been used to induce radical cyclization with alkyl iodides, and constitutes a tin-free procedure for radical iodine atom transfer reactions.¹¹⁴



Formation of the five-membered ring via a 5-exo-trig reaction is a kinetic process. With the possibility of a larger or a smaller ring, radical cyclization generally gives the smaller ring. There is a better SOMO-LUMO overlap ($\approx 109^{\circ}$ angle of attack) than is possible in the 6-endo-trig transition state, which favors the 5-exo-trig preference. Beckwith¹¹⁵ calculated the transition state strain energies for radical cyclization of ω -alkenyl radicals H₂C=CH(CH₂)_nCH₂•, and found that the energy increased as the size of the ring being formed increased (i.e., the value of

^{112.} For a review of the synthesis of medium-sized rings using free radical conditions, see Yet, L. *Tetrahedron* 1999, 55, 9349.

^{113.} Reference 11, p 419.

^{114.} Ollivier, C.; Bark, T.; Renaud, P. Synthesis 2000, 1598.

Beckwith, A.L.J.; Ingold, K.U. in Vol 1 of *Rearrangements in Ground States and Excited States*, de Mayo, P. (Ed.), Academic Press, New York, *1980*, pp 162-283.

n increased).¹¹⁶ The ΔE_s for the exo transition state is lower in energy than the corresponding endo transition state, except for octenyl radical and 2-methyl-1-hexenyl radical. The former reflects the difficulty in forming eight-membered rings, and the latter reflects the increase in steric strain due to the methyl group. Beckwith used **141** as the model for exo-trig ring closure, and **142** as the model for endo-trig ring closure.¹¹⁶



[Reprinted with permission from Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron Lett.* **1985**, *26*, 373, Copyright 1985, with permission from Elsevier Science.]



In the presence of AIBN and Bu₃SnH, 6-bromo-1-hexene reacts with AIBN to give the hex-5-enyl radical. This may either abstract hydrogen from Bu₃SnH, leading to the unrearranged reduction product, 1-hexene, or first cyclize either to cyclopentylmethyl radical or to cyclohexyl radical before abstracting hydrogen, leading to methylcyclopentane and cyclohexane, respectively. Experimentally, the ratio of 1-hexene:methylcyclopentane:cyclohexane is 17:81:2.



Calculations show that the barrier for closure to cyclohexyl radical is 10 kJ/mol larger than that for closure to cyclopentylmethyl radical. Assuming that there is no unrearranged product, this corresponds to a ratio of cyclopentylmethyl to cyclohexyl radicals of 95:5. Does this support the notion that the ring closure reaction is kinetically controlled? Examine the transition states that are provided on screen for the ring closure reactions leading to the two radicals. Are there are structural differences that might explain the noted preference?

Obtain energies for both cyclohexyl to cyclopentylmethyl radicals. For each in turn, *click* on > to the right of the tab at the top of the screen and select *Continue*. A radical may be built from its corresponding products by deleting the appropriate hydrogen atom. Which radical is more stable? Why? Were the reaction under thermodynamic control, what would the ratio of the products be at room temperature (assume that there is no unrearranged product)? Does your result support the notion that the ring closure reaction is thermodynamically controlled?

^{116. (}a) Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron Lett.* **1985**, *26*, 373; (b) Beckwith, A.L.J. *Tetrahedron* **1981**, *37*, 3073.



This preference is seen for the cyclization reaction of **143**, where the five-membered ring radical product (**144**) predominated with a variety of substituents R rather than the cyclohexyl radical (**145**).¹¹⁷ When R is

hydrogen or an alkyl group, the ratio of **144/145** is >95:5. That ratio is 93:7 when R is CO_2R^1 , and about 75:25 when R is COR or COPh.¹¹⁷ Another potential problem with this reaction is formation of cis or trans isomers. In Table 13.3,¹¹⁷ iodoalkene **146** gives essentially a 1:1 mixture of cis (**147**) and trans (**148**) products under a variety of conditions, but the 6-endo-trig product (**149**) is formed as a minor constituent. In the absence of special controlling factors (steric, electronic, neighboring group effects, etc.) the cyclization proceeds with poor cis-trans selectivity.

$I \xrightarrow{I}_{CO_2Me} \xrightarrow{0.3 \text{ M}, PhH} I$	$\begin{array}{c} & & \\ & & \\ & & \\ & & \\ 147 \end{array} + \begin{array}{c} & & \\ & & $	$Me^{H} + MeO_2C - M$			
Conditions	<u>% Yield</u>	<u>147 : 148 : 149</u>			
10% Bu ₃ SnH, AIBN, 5h	48	48:45:7			
10% AIBN, 24h	78	49:43:8			
Me ₃ Sn-SnMe ₃ , heat, 16h	83	53:40:7			
Bu ₃ Sn-SnBu ₃ , hv, 24h	42	50:40:10			
[Reprinted with permission from Curran, D.P.; Chang, CT. J. Org. Chem. 1989, 54, 3140. Copyright © 1989 American Chemical Society.]					

 Table 13.3
 cis-trans
 Selectivity in the Radical Cyclization of 146

In the formation of polycyclic systems, the cyclization process can lead to more than one regioisomer or stereoisomer. As noted in Table 13.3, the ratio of (*E*) and (*Z*) isomers is often ~1:1. In most cyclizations, cis-ring fusion predominates when the final product is a bicyclo[3.3.0]- or bicyclo[4.3.0]-system, but formation of a bicyclo[5.3.0]-system usually leads to significant amounts of trans-fused products.¹¹⁸ In the cyclization of **150**, a mixture of (*E*) and (*Z*) isomers is possible, and there are two different alkene moieties in **150** that lead to different regioisomeric products.¹¹⁸ Abstraction of the bromide in **150** with Bu₃Sn• generated a radical



that cyclized, and was quenched with tin hydride via hydrogen transfer to give a 1:1 mixture of **151/152** in 89% yield. Note that there are diastereomers resulting

from the presence of OMe and the ratio of α/β -methoxyl isomers in **152** was 3:1.¹¹⁹ All products were cis fused. The reaction was controlled by frontier molecular orbitals (SOMO-LUMO, sec. 13.4) rather than stabilities of radical intermediates.

^{117.} Curran, D.P.; Chang, C.-T. J. Org. Chem. 1989, 54, 3140.

^{118. (}a) Reference 11, p.421; (b) Clive, D.L.J.; Cheshire, D.R.; Set, L. J. Chem. Soc. Chem. Commun. 1987, 353.

^{119.} Beckwith, A.L.J.; O'Shea, D.M.; Roberts, D.H. J. Chem. Soc. Chem. Commun. 1983, 1445.

There are many synthetic examples that use radical cyclization as a key step, and the radical precursor is not limited to unfunctionalized alkyl iodides or bromides. In Lee and co-worker's synthesis of (+)-IKD-8344,¹²⁰ the primary bromide unit on the silyloxy tether of **153** was cyclized to give **154** in 91% yield. Note the use of triethylborane as the radical initiator. Cyclization via aryl radicals is also possible. In a synthesis of (+)-dinapsoline by Sit and co-workers¹²¹ aryl bromide **155** was cyclized to **156** in good yield under standard conditions in degassed benzene. Radical cascade reactions can be used for the synthesis of polycyclic ring systems. In these reactions, polyenes are subjected to radical cyclization, generating tricyclic or even tetracyclic ring systems.¹²² Chiral auxiliaries have been used effectively in radical cyclization reactions.¹²³



Alkynes are common precursors to *exo*-methylene compounds, as in Sha and co-worker's synthesis of (–)-bakkenolide.¹²⁴ Treatment of iodide **157** with tributyltin dimer and then AIBN/ Bu₃SnH led to the radical intermediate and cyclization. The second step was required to reduce the iodide formed in the first reaction of the radical by tributyltin hydride to give a 93% yield of **158**. The trimethylsilyl group attached to the alkyne unit is important to sterically inhibit a 6-endo-dig reaction that can complete with the 5-exo-dig process. The silyl group in **158** was removed by treatment with trifluoroacetic acid in dichloromethane, giving **159** in 80% yield along with 10% of the conjugated ketone in which the C=C unit migrated to the endocyclic position.



120. Kim, W.H.; Hong, S.K.; Lim, S.M.; Ju, M.-A.; Jung, S.K.; Kim, Y.W.; Jung, J.H.; Kwon, M.S.; Lee, E. *Tetrahedron* 2007, 63, 9784.

- 121. Sit, S.-Y.; Xie, K.; Jacutin-Porte, S.; Taber, M.T.; Gulwadi, A.G.; Korpinen, C.D.; Burris, K.D.; Molski, T.F.; Ryan, E.; Xu, C.; Wong, H.; Zhu, J.; Krishnananthan, S.; Gao, Q.; Verdoorn, T.; Johnson, G. J. Med. Chem. 2002, 45, 3660.
- 122. For examples, see (a) Boehm, H.M.; Handa, S.; Pattenden, G.; Roberts, L.; Blake, A.J.; Li, W.-S. J. Chem. Soc. Perkin Trans. 1 2000, 3522; (b) Fensterbank, L.; Mainetti, E.; Devin, P.; Malacria, M. Synlett, 2000, 1342.
- 123. For an example taken from a synthesis of (+)-triptocallol, see Yang, D.; Xu, M.; Bian, M.-Y. *Org. Lett.* **2001**, *3*, 111.
- 124. Jiang, C.-H.; Bhatacharyya, A.; Sha, C.-K. Org. Lett. 2007, 9, 3241.

Vinyl radicals are useful in radical coupling and addition reactions.¹²⁵ Stork used the cyclization of vinyl radical **161** (derived from vinyl bromide **160**) to complete a synthesis of norseychellanone (**162**).¹²⁶ The cyclization step proceeded in 70% yield. Coupling one aromatic ring to another is also possible using radical techniques. In a synthesis of goniopedaline,¹²⁷ Couture and co-workers refluxed **163** with AIBN and Bu₃SnH in benzene and obtained a 75% yield of **164**.



The radical cyclization disconnections are



13.7.B. Heteroatom Ring Systems

Radical cyclization can be used to prepare many heterocyclic rings.¹²⁸ The standard AIBN and tributyltin hydride in refluxing benzene conditions are common, but other solvents can also be used. For instance, radical cyclization of **165** in aqueous ethanol using a combination of phosphoric acid and a base led to **166** in 83% yield.¹²⁹ In this example, it is clear that

- 127. Rys, V.; Couture, A.; Deniau, E.; Grandclaudon, P. Eur. J. Org. Chem. 2003, 1231.
- 128. (a) Majumdar, K.C.; Basu, P.K.; Mukhopadhyay, P.P. *Tetrahedron*, *2004*, *60*, 6239; (b) Bowman, W.R.; Fletcher, A.J.; Potts, G.B.S. J. Chem. Soc. Perkin Trans. 1 2002, 2747.
- 129. Yorimitsu, H.; Shinokubo, H.; Oshima, K. Chem. Lett. 2000, 104.

^{125. (}a) Stork, G.; Baine, N.H.. Am. Chem. Soc. 1982, 104, 2321; (b) Stork, G.; Mook, Jr., R. Ibid. 1983, 105, 3720; (c) Nozaki, K.; Oshima, K.; Utimoto, K. Ibid. 1987, 109, 2547; (d) Stork, G.; Mook, Jr., R. Ibid. 1987, 109, 2829; (e) Beckwith, A.L.J.; O'Shea, D.M. Tetrahedron Lett. 1986, 27, 4525; (f) Stork, G.; Mook, Jr., R. Ibid. 1986, 27, 4529.

^{126.} Stork, G.; Baine, N.H. Tetrahedron Lett. 1985, 26, 5927.

heteroatoms can be part of the chain that links the radical precursor and the alkene. Stork prepared protected lactones via radical cyclization of alkenyl ethers.¹³⁰ White and coworkers used this reaction in a synthesis of rhizoxin D.¹³¹ Cyclization of **167** gave **168A** and **168B**, but the nature of R¹ and R² played a key role in the cyclization. Cyclization of **167** (R¹= H, R² = CO₂Me) gave essentially a 1:1 mixture of anti (**168A**) and syn (**168B**) diastereomers in 92% yield. When **167** (R¹ = CO₂Me, R² = H) was similarly cyclized, however, a 15:1 mixture of anti:syn (**168A**:**168B**) diastereomers was obtained in 93% yield. The electron withdrawing carbomethoxy group facilitated formation of the six-membered ring. The position of the CO₂Me unit influenced the transition state of cyclization, where the transition state for cyclization of *Z*-ester showed a marked preference for a less hindered conformation that led to high diastereoselectivity.¹³²



Heterocyclic rings can be prepared by simply incorporating a heteroatom into the chain, as in the cyclization of **165** to **166** or **167** to **168**. An example with a nitrogen in the molecule was reported by Koreeda and co-workers in a synthesis of (–)-sibirine.¹³³ Reaction of selenide **169** with AIBN/Bu₃SnH in refluxing toluene led to a close to 1:1 mixture of the 5-exo-trig product **170** and the 7-endo-trig product, **171**. Based on Baldwin's rules (sec. 6.6.A), it is clear that there is little difference in the transition state energies leading to the two products.



 ⁽a) Stork, G.; La Clair, J.J.; Spargo, P.; Nargund, R.P.; Totah, N. J. Am. Chem. Soc. 1996, 118, 5304. Also see (b) Stork, G.; Mook Jr., R.; Biller, S.A.; Rychnovsky, S.D. J. Am. Chem. Soc. 1983, 105, 3741.

- 132. Ishibashi, H.; Matsukida, H.; Toyao, A.; Tamura, O.; Takeda, Y. Synlett 2000, 1497.
- 133. Koreeda, M.; Wang, Y.; Zhang, L. Org. Lett. 2002, 4, 3329.

^{131.} White, J.D.; Blakemore, .R.; Green, N.J.; Hauser, E.B.; Holoboski, M.A.; Keown, L.A.; Kolz, C.S.N.; Phillips, B.W. J. Org. Chem. 2002, 67, 7750.

Both phenylthio (-SPh) and phenylseleno (-SePh) groups can be used as leaving groups for radical cyclization (see above), where sulfur or selenium atom transfer leads to radical formation. Hart and Tsai used this technique to cyclize **172** to the racemic diastereomer **173** in a synthesis of isoretronecanol.^{134c} Smith and co-workers, however, used a chiral template approach and prepared alkenyl iodide **174** from the chiral precursor pyroglutamate.¹³⁵ Radical cyclization gave pyrrolizidinone **175** in a synthesis of pseudoheliotridane, with high asymmetric induction.¹³⁵ Knapp et al. also used pyroglutamate derivatives for asymmetric radical cyclizations.¹³⁶ Other heterocycles can be used in radical cyclizations.¹³⁷ Treatment of pyrrole derivative **176** with AIBN and tributyltin hydride gave a 60% yield of **177**. The sulfonyl group on the pyrrole ring was required for good yields of cyclized product.¹³⁸



Radical cyclization with high diastereoselectivity and high asymmetric induction is possible when chiral precursors are used (as with $174 \rightarrow 175$ from pyroglutamate). Livinghouse and Jolly¹³⁹ reported a chiral synthesis of (–)-trachelanthamidine via cyclization of **178**, prepared



from prolinal, which gave a 30:1 mixture of **179** and **180** in 55% yield. In this reaction, initiation with AIBN in the presence of tri-*n*-butyltin hydride led to significant

amounts of the hydrogen transfer product (2-ethenyl-*N*-acetyl-2-pyrrolidinone). Hydrogen transfer is a common problem, and it was solved in this work by changing the method by which the radical is generated. Radical cyclization in the presence of tributyltin dimer (Bu₃SnSnBu₃) gave the desired products (as shown), but required photochemical initiation with a sunlamp.

- 136. Knapp, S.; Gibson, F.S.; Choe, Y.H. Tetrahedron Lett. 1990, 31, 5397.
- 137. Bowman, W.R.; Bridge, C.F.; Brookes, P. J. Chem. Soc. Perkin Trans. 1 2000, 1.
- Antonio, Y.; de la Cruz, E.; Galeazzi, E.; Guzman, A.; Bray, B.L.; Greenhouse, R.; Kurz, L.J.; Lustig, D.A.; Maddox, M.L.; Muchowski, J.M. Can. J. Chem. 1994, 72, 15.
- 139. Jolly, R.S.; Livinghouse, T. J. Am. Chem. Soc. 1988, 110, 7536.

^{134. (}a) Choi, J.-K.; Hart, D.J.; Tsai, Y.-M. *Tetrahedron Lett.* 1982, 23, 4765; (b) Burnett, D.A.; Choi, J.-K.; Hart, D.J.; Tsai, Y.-M. J. Am. Chem. Soc. 1984, 106, 8201; (c) Hart, D.J.; Tsai, Y.-M. *Ibid.* 1982, 104, 1430; (d) *Idem Ibid.* 1984, 106, 8209; (e) Choi, J.-K.; Hart, D.J. *Tetrahedron* 1985, 41, 3959.

^{135. (}a) Keusenkothen, P.F.; Smith, M.B. J. Chem. Soc. Perkin Trans. 1 1994, 2485; (b) Keusenkothen, P.F.; Smith, M.B. Tetrahedron Lett. 1989, 30, 3369.

MOLECULAR MODELING: Experiments and Calculations are both Similar and Different

Experiments and calculations are both able to provide information about structures, energies and properties. Experiments "report" chemistry, whereas calculations simulate (model) the fundamental processes underlying chemistry. Neither experiments nor calculations tell "why" something happens, for example, why one product is favored over another. What chemists might explain in terms of simple language ("this is more crowded than that") may in fact be much more complicated.

Radical cyclization of the *E*-conjugated ester (**A**) gives a 1:1 mixture of *syn* and *anti* diastereomers in >90% yield. Cyclization of the corresponding *Z*-conjugated ester (**B**) under the same conditions gives the same products, but in a 15:1 mixture of *anti:syn* diastereomers.



Transition state calculations reproduce these results. The *syn* and *anti* transition states for the reaction of **A** are separated by less than 1 kJ/mol, while the *syn* transition state for the reaction of **B** is 13/kJ below the *anti* transition state. Examination of the transition states for both reactions ($\mathbf{A} \rightarrow syn$, top left; $\mathbf{A} \rightarrow anti$, top right; $\mathbf{B} \rightarrow syn$, bottom left; $\mathbf{B} \rightarrow anti$, bottom right), however, does *not* reveal the cause of the individual preferences or for the change in preference from *E* to *Z* alkenes.

You can expect modeling to help you assign major and minor products, determine whether the reaction is under kinetic or thermodynamic control, estimate reactivity as well as regio and stereoselectivity, and compare products and rates of one reaction with another. Don't expect the models to tell you why. If a synthetic chemist needs to modify product distribution, an understanding of mechanism is essential. Thoughtful experiments will usually be necessary, often in combination with thoughtful modeling.

The use of dibutyltin dimer under photochemical methods is an atom-transfer method that is most useful when the cyclization step is slow (see above). When cyclization is slow relative to hydrogen transfer, the dominant reaction is usually hydrogen atom transfer to give reduced products. Photolysis of the tin dimer generates the radical intermediate without a hydrogen atom transfer agent present (other than the substrate and the solvent). Another example illustrating the utility of this reagent in cyclization reactions is Curran and Chang's attempt to cyclize **181**, which gave only **182** on treatment with tin hydride/AIBN and no **183**.¹⁴⁰ Cyclization with dibutyltin dimer and photochemical induction gave a radical intermediate that was quenched by reaction with the iodine radical byproduct to give **183**. The iodine could be reduced by reaction with tin hydride (see sec. 13.5D).¹⁴⁰

^{140.} Curran, D.P.; Chang, C.-T. Tetrahedron Lett. 1987, 28, 2477.



MOLECULAR MODELING: Thermodynamic vs. Kinetic Control Revisited

Reaction of **A** with AIBN gives rise to the radical **B**, which then cyclizes either to a cyclohexyl radical (**C**) via pathway a, or to a tetrahydropyranyl radical (**D**) via pathway b. The products are **E** and **F**, respectively. Experimentally, the ratio of **E**:**F** is 1:3 (pathway b is favored).



Calculations show that the barrier to **D** is 3 kJ/mol less than that to **C**. This does not necessarily mean that this reaction is under kinetic control, as **D** may also be the thermodynamic product. Obtain energies for **C** and **D**. Start with **E** and **F**, and delete the appropriate hydrogen atom. Is **D** the thermodynamic product? Is the cyclization necessarily kinetically controlled? Elaborate.

Where cyclization involves formation of a six-membered ring, allylic hydrogen abstraction may be preferred. Attempted cyclization of **184** gave only **187** via hydrogen abstraction (**179** to **180**), and no cyclization was observed.¹⁴¹ A six-center transition state for removal of the allylic hydrogen is possible in **185**, and this is preferred over the 6-exo-trig transition state for ring formation. The methyl groups in **185** prevent close approach of hydrogen to the radical center. If an activating group is attached to the alkene receptor, formation of the six-membered ring is accelerated relative to hydrogen transfer.



Bach and co-workers reported an asymmetric radical cyclization,¹⁴² in which alkenyl-iodide **188** cyclized under radical conditions (initiated by BEt₃) in the presence of the chiral complexing

^{141.} Leonard, W.R.; Livinghouse, T. Tetrahedron Lett. 1985, 26, 6431.

^{142.} Aechtner, T.; Dressel, M.; Bach, T. Angew. Chem. Int. Ed. 2004, 43, 5849.

agent **189**. The selectivity is believed to rise from hydrogen-bond mediation of the radical cyclization in the presence of **189**. Under these conditions, cyclization of **188** gave a 71% yield of **190** in 79% ee.



Radical conjugate additions of this type are very facile, and many internal cyclizations have been reported.¹⁴³ Relatively large rings can be prepared, as illustrated by the cyclization of **191** to **192** and **193** (63% and 22% yield, respectively).¹⁴⁴ The cyclization process is faster than the hydrogen transfer under high dilution conditions. The two remote reactive fragments of the long chain must be in close proximity for the cyclization.



The alkenyl and alkynyl radical disconnections are

$$(CH_2)_n \xrightarrow{R} (CH_2)_n \xrightarrow{R}$$

Samarium (II) iodide mediates radical-type cyclizations, and has been used in the synthesis of natural products.¹⁴⁵ Two examples illustrate the utility, and similarity to the transformations described above. Curran and co-workers shown that aryl ether **194** reacted with SmI₂ to give the cyclized product, and quenching with D₂O provide benzofuran **195** in 80% yield.¹⁴⁶ Ohta and co-workers used this type of strategy for a synthesis of pyrrolam A.¹⁴⁷ Alkynyl lactam **196** was treated with excess SmI₂, leading to a 90% yield of cyclized product, indolizidinone **197**.



^{143.} For example, see Winkler, J.D.; Sridar, V. Tetrahedron Lett. 1988, 29, 6219.

- 144. Porter, N.A.; Chang, V.H.-T. J. Am. Chem. Soc. 1987, 109, 4976.
- 145. Edmonds, D.J.; Johnston, D.; Procter, D.J. Chem. Rev. 2004, 104, 3371.
- 146. Curran, D.P.; Fevig, T.L.; Totleben, M.J. Synlett 1990, 773.
- 147. Aoyagi, Y.; Manabe, T.; Ohta, A.; Kurihara, T.; Pang, G.-L.; Yuhara, T. Tetrahedron 1996, 52, 869.

13.7.C Cyclization to C=X and Cyclization of Heteroatom Radicals



Radical cyclization is not limited to addition to alkenes and alkynes. Carbonyls and imines can also be radical receptors. Enholm and co-workers showed that when

198 was treated with AIBN and tributyltin hydride, the major product was a mixture of alcohols **199** and **200**.¹⁴⁸ Fu and Hays showed that this could be made catalytic in tributyltin hydride.¹⁴⁹ When **198** was treated with 0.1 Bu₃SnH, 0.5 PhSiH₃, two equivalents of EtOH and AIBN, an 85% yield was obtained as a 1.1:1 **199/200** mixture.

In Keck and co-worker's synthesis of 7-deoxypancratistatin, radical precursor **201** was cyclized to the oximine ether unit under radical conditions to give a 3:1 mixture of **202** and **203** in 90% yield.¹⁵⁰ Another variation by Weinreb and co-workers involving generation, cyclization, and trapping of amidyl radicals.¹⁵¹ When hydroxamic acid **204** was cyclized with TEMPO in the presence of diphenyl diselenide, lactam **205** was obtained in 64% yield.



The C=X radical cyclization disconnection is



A classical named reaction provides another example of a hydrogen atom transfer reaction that produces a heterocyclic compound. When N-halo-amines¹⁵² such as **206** are treated with

^{148. (}a) Enholm, E.J.; Prasad, G. *Tetrahedron Lett.* 1989, 30, 4939; (b) Enholm, E.J.; Burroff, J.A. *Tetrahedron Lett.* 1992, 33, 1835; (c) Enholm, E.J.; Burroff, J.A. *Tetrahedron*, 1997, 53, 13583; (d) Enholm, E.J.; Kinter, K.S. J. Org. Chem. 1995, 60, 4850.

^{149.} Hays, D.S.; Fu, G.C. Tetrahedron 1999, 55, 8815.

^{150.} Keck, G.E.; McHardy, S.F.; Murry, J.A. J. Org. Chem. 1999, 64, 4465.

^{151.} Lin, X.; Stien, D.; Weinreb, S.M. Tetrahedron Lett. 2000, 41, 2333.

^{152.} Kovacic, P.; Lowery, M.K.; Field, K.W. Chem. Rev. 1970, 70, 639.

concentrated sulfuric acid, the amino radical cation **207** is produced. Hydrogen atom transfer via a six-center transition state generates the ammonium radical (**208**), which reacts with the protonated form of **206** (ammonium salt **209**) to give **210**. When **210** is neutralized, the amine displaces the primary halide to give a hexahydroindolizine (**211**).¹⁵³ The conversion of *N*-haloamines to cyclic amines is called the **Hofmann-Löffler-Freytag reaction**.¹⁵⁴



In its original form, the reaction generated pyrrolidine derivatives and other cyclic amines as in the conversion of **212** to **213**. Treatment with a base generated the free amine, and subsequent nucleophilic displacement of chloride (cyclization) led to **214** as the final product. This acid mediated reaction can be initiated or photochemically.¹⁵⁵ as in the conversion of **215** to **216** in 99 x 53% overall yield, taken from Sanz-Cervera and Williams' synthesis of (–)-VM55599.¹⁵⁶ Initial *N*-chlorination of the primary amine (to give a 99% yield of the chloroamine) was followed by irradiation in sulfuric acid. The final step was basification to generate the pyrrolidine (in this case a proline) derivative, and protection of the nitrogen as a *tert*-butylcarbamate (*N*-Boc, see sec. 7.3.C.iii). The high temperatures required in older versions of this conversion can lead to poor stereoselectivity. One solution to this problem is to use a mixture of cuprous chloride and cupric chloride (CuCl–CuCl₂) in acidic media to effect cyclization.¹⁵⁷



^{153.} Corey, E.J.; Hertler, W.R. J. Am. Chem.Soc. 1960, 82, 1657.

157. Broka, C.A.; Eng, K.K. J. Org. Chem. 1986, 51, 5043.

^{154. (}a) Hofmann, A.W. Berichte 1883, 16, 558; (b) Idem Ibid. 1885, 18, 5; (c) Löffler, K.; Freytag, C., Ibid. 1909, 42, 3427; (d) Wolff, M.E. Chem. Rev. 1963, 63, 55; (e) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-45; (f) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 328-329.

^{155.} Furstoss, R.; Teissier, P.; Waegell, B. Tetrahedron Lett. 1970, 1263.

^{156.} Sanz-Cervera, J.; Williams, R.M. J. Am. Chem. Soc. 2002, 124, 2556.

The Hofmann-Löffler-Freytag disconnection is



13.7.D Bergman Cyclization

Ene-diynes undergo a cycloaromatization reaction that is formally a thermally allowed electrocyclic reaction. In principle, this reaction belongs in Chapter 11, but it is known that the reaction proceeds by a diradical. For that reason and since a ring is formed it is placed in this



 $\begin{array}{c} \begin{array}{c} \text{section, although it is not formally a radical} \\ \text{cyclization. In a generic example, ene-diyne} \\ \textbf{219} \\ \begin{array}{c} \text{section, although it is not formally a radical} \\ \text{cyclization. In a generic example, ene-diyne} \\ \textbf{217 cyclizes to give diradical 218, which loses} \\ \text{two hydrogen atoms via aromatization to give} \\ \text{the benzene ring in 219. This conversion of} \end{array}$

an ene-diyne to a benzene derivative is called the **Bergman cyclization**.¹⁵⁸ The activation barrier for this process can be greatly influenced by electronic substituent effects.¹⁵⁹ A metal-accelerated Bergman cycloaromatization has been reported, using an arene complex, $[(\eta^5-C_5Me_5)Ru(\eta^6-3,4-benzocyclodec-3-ene-1,5-diyne][OTf].^{160}$ This reaction has taken on great importance with the discovery that the biological action of several anticancer antibiotics [calicheamicin, dynemicin, esperamicin, and kedarcidin] is linked to Bergman cyclization of an ene-diyne core structure accompanying cleavage of double-stranded DNA.¹⁶¹

From a purely synthetic viewpoint, the radicals generated by the Bergman cyclization have been used to initiate further cyclization, including the preparation of aromatic compounds. In one example, Jones and Plourde prepared a series of chlorinated ene-diynes and used the Bergman cyclization to convert them to chlorinated aromatic compounds.¹⁶² Heating **220**, for example, gave a 40% yield of **221**.¹⁶² Interestingly, heating **220** with tetramethylpiperidinyloxy free radical (TEMPO) led to a 30% yield of the chlorinated benzoquinone **222**. The additional chorine atoms in **221** are attributed to atom transfer chemistry from carbon tetrachloride to the diradical intermediate. This reaction is not limited to carbocyclic compounds, and an aza-

162. Jones, G.B.; Plourde, II, G.W. Org. Lett. 2000, 2, 1757.

⁽a) Jones, R.R.; Bergman, R.G. J. Am. Chem. Soc. 1972, 94, 660; (b) Bergman, R.G. Acc. Chem. Res. 1973, 6, 25; (c) Darby, N.; Kim, C.U.; Shelton, K.W.; Takada, S.; Masamune, S. J. Chem. Soc. (D) 1971, 23, 1516; (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-9; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 90-91.

^{159.} Schmittel, M.; Kiau, S. Chem. Lett. 1995, 953.

^{160.} O'Connor, J.M.; Lee, L.I.; Gantzel, P. J. Am. Chem. Soc. 2000, 122, 12057.

 ⁽a) Nicolaou, K.C.; Stabila, P.; Esmaeli-Azad, B.; Wrasidlo, W.; Hiatt, A. *Proc. Natl. Acad. Sci., USA* 1993, 90, 3142; (b) Zein, N.; Solomon, W.; Casazza, A.M.; Kadow, J.F.; Krishnan, B.S.; Tun, M.M.; Vyas, D.M.; Doyle, T.W. *Bioorg. Med. Chem. Lett.* 1993, 3, 1351.

Bergman rearrangement reaction has been reported.¹⁶³



13.8 METAL-INDUCED RADICAL REACTIONS

13.8.A General Principles

Metal-induced radical reactions can take at least two forms: (1) electron transfer of a metal to a peroxide, leading to reactive free radicals, and (2) direct electron transfer from a metal to an alkene, carbonyl or aromatic substrate. An example of the first type of reaction is oxidation with **Fenton's reagent** (sec. 3.3.A),¹⁶⁴ which initiates oxidation of aryls to phenols, although the yields are usually only 5-20%. In this reaction, ferrous ion (Fe²⁺) is oxidized to ferric ion (Fe³⁺) by hydrogen peroxide which gives hydroxide and hydroxyl radicals (HO•).¹⁶⁴ The presence of the radicals initiates a chain process, which can be terminated by reaction of HO• with Fe²⁺. Oxidation of benzene with Fenton's reagent gave only a small amount of phenol, but large amounts of biphenyl, arising from coupling of the aryl radicals. Another metal system is Ti³⁺-H₂O₂ (at pH 2), which generates HO• and HOO• radicals.¹⁶⁵ Transition metals such as titanium, cobalt or manganese are often used in conjunction with hydroperoxides, and decompose under these conditions to alkoxy radicals (RO•) and alkyl peroxyls (ROO•).^{164a,166} In all cases, reaction with the metal generates a radical, which then reacts with the carbon fragment to induce the desired radical reaction. The latter metal-peroxide reaction was discussed previously in section 3.4.B in connection with the transition metal-peroxide oxidation of alkenes to oxiranes.¹⁶⁷

13.8.B Phenolic Oxidative Coupling

A classical oxidation reaction that involves radicals is the **phenolic oxidative coupling**,¹⁶⁸ which is introduced in Section 10.5.A.i. In this reaction, electron transfer from a metal salt to a bis(phenol) leads to intramolecular coupling and a quinone product. In early experiments, yields were poor. For example, Barton and Kirby reacted **223** with potassium ferricyanide [K₃(Fe(CN)₆]

^{163.} Feng, L.; Kumar, D.; Kerwin, S.M. J. Org. Chem. 2003, 68, 2234.

⁽a) Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, London, *1985*, p 173;
(b) Smith, J.R.L.; Norman, R.O.C. *J. Chem. Soc. 1963*, 2897.

^{165. (}a) Reference 4, p 31; (b) Irvine, M.J.; Wilson, I.R. Aust. J. Chem. 1979, 32, 2131, 2283.

^{166.} Black, J.F. J. Am. Chem. Soc. 1978, 100, 527.

^{167.} Hiatt, R. in Oxidation, Vol. 2, Augustine, R.L.; Trecher, D.J. (Eds.), Marcel Dekker, New York, 1971, pp 117-124.

^{168. (}a)Barton, D.H.R.; Deflorin, A.M.; Edward, O.E.J. Chem. Soc. 1956, 530; (b) Scott, A.I. Quart. Rev. 1965, 19, 1.

and the initial product was aryl radical **224**. This radical reacted with the second phenolic ring in an intramolecular process that gave **225**. Loss of a hydrogen atom led to the quinone narwedine (**226**), as part of a synthesis of galanthamine.¹⁶⁹ The yield of **226**, however, was only 1.4% under optimal conditions. Kametani and co-workers improved the yield of the oxidation only slightly (5% yield) by using an amide derivative of **223**, in a synthesis of galanthamine.¹⁷⁰



A similar oxidation procedure was used by Gervay et al. to generate erythrinadienone in 35% yield,¹⁷¹ which constituted a great improvement in the yield. The yield remained relatively low, however, due to the shortness of the tether between the two aryl moieties or from the steric hindrance provided by the hydroxyl and alkoxyl groups.¹⁷² Indeed, success for phenolic oxidative coupling is dependent on the nature of the substituents on the aromatic rings, as well as the length of the tether.¹⁷³ Other oxidative methods can be used, including anodic oxidation under electrolysis conditions. Good yields can be obtained in such systems, as in the anodic oxidation of tetramethoxy derivative **227** to give **228** in 80% yield, where **228** was a key intermediate in Tobinaga and co-worker's synthesis of colchicine.¹⁷² In another variation, Stevenson and co-workers used VOF₃ to convert **229** to deoxyschizandrin (**230**) in 54% yield.¹⁷⁴ Phenyliodine (III)bis(trifluoroacetate) has also been used to effect phenolic oxidative coupling,¹⁷⁵ as have other hypervalent iodine (II) reagents.¹⁷⁶ In a synthesis of (+)-puupehenone, Quideau and co-workers¹⁷⁷ treated **231** with [bis(trifluoroacetoxyiodo]benzene and obtained a 67% yield of **232**.

^{169.} Barton, D.H.R.; Kirby, G.W. J. Chem. Soc. 1962, 806.

^{170. (}a) Kametani, T.; Shishido, K.; Hayashi, E.; Seino, C.; Kohno, T.; Shibuya, S.; Fukumoto, K. *J. Org. Chem.* 1971, 36, 1295; (b) Kametani, T.; Seino, C.; Yamaki, K.; Shibuya, S.; Fukumoto, K.; Kigasawa, K.; Satoh, F.; Hiiragi, M.; Hayasaka, T. *J. Chem. Soc. C* 1971, 1043; (c) Kametani, T.; Yamaki, K.; Yagi, H.; Fukumoto, K. *Ibid.* 1969, 2602.

 ^{171. (}a) Gervay, J.E.; McCapra, F.; Money, T.; Sharma, G.M.; Scott, A.I. J. Chem. Soc. Chem. Commun. 1966, 142; (b) Mondon, A.; Ehrhardt, M. Tetrahedron Lett. 1966, 2557.

^{172. (}a) Kotani, E.; Miyazaki, F.; Tobinaga, S. J. Chem. Soc. Chem. Commun. 1974, 300; (b) Tobinaga, S.; Kotani, E. J. Am. Chem. Soc. 1972, 94, 309.

^{173.} See for example, Krauss, A.S.; Taylor, W.C. Aust. J. Chem. 1992, 45, 925, 935.

^{174.} Biftu, T.; Hazra, B.G.; Stevenson, R. J. Chem. Soc. Perkin Trans. 1 1979, 2276.

^{175.} Kita, Y.; Gyoten, M.; Ohtsubo, M.; Tohma, H.; Takada, T. Chem. Commun. 1996, 1481.

 ^{176. (}a) Quideau, S.; Pouységu, L. Org. Prep. Proc. Int. 1999, 31, 617; (b) Quideau, S.; Pouységu, L.; Oxoby, M.; Looney, M.A. Tetrahedron 2001, 57, 319.

^{177.} Quideau, S.; Lebon, M.; Lamidey, A.-M. Org. Lett. 2002, 4, 3975.



Note that many phenolic coupling reactions may proceed via radical cation intermediates and/ or phenoxonium ions, especially when the coupling is induced by electrochemical methods. In such cases, it is not always clear that the mechanism involves a radical-radical coupling reaction.

The phenolic oxidative coupling disconnection is



13.8.C Copper-Catalyzed Coupling Reactions

Many methods have been developed that form an aryl-aryl bond,¹⁷⁸ including the metalcatalyzed radical reaction known as **Meerwein arylation**.¹⁷⁹ This reaction combines an aryl diazonium salt (such as phenyldiazonium chloride, **233**) with an electron-deficient alkene (containing an electron-withdrawing group such as carboethoxy in ethyl acrylate) to give the phenyl-substituted acrylate derivative (**235**) with a cupric chloride (CuCl₂) catalyst. Under these conditions, CuCl₂ induces loss of nitrogen (N₂) from **233** to give the aryl radical (**16**), and formation of this radical is followed by addition to the alkene to give **234**. Subsequent reaction of this reactive intermediate with CuCl₂ generated the alkene (**235**) via loss of HCl, also generating CuCl. This reaction is obviously similar to the Heck reaction discussed in

^{178.} Hassan, J.; Savignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. Chem. Rev. 2002, 102, 1359.

 ⁽a) Meerwein, H.; Büchner, E.; van Emster, K. J. Prakt. Chem. 1939, 152, 237; (b) Rondestvedt, Jr., C.S. Org. React. 1960, 11, 189; (c) Idem Ibid. 1976, 24, 225; (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-59.

section 12.7.A. Titanium trichloride (TiCl₃) has been used to initiate 1,4 addition to conjugated carbonyl derivatives.¹⁸⁰



There are many variations, and a wide range of aromatic diazonium salts can be used. One method for generating the diazonium salt is treatment of an aromatic amine with nitrous acid (HONO via reaction of HNO₃/HCl or NaNO₂/2 HCl.¹⁸¹ The coupling of diazonium salts to other aromatic compounds¹⁸² in the presence of base is commonly called the **Gomberg-Bachmann reaction**. Treatment of 4-bromoaniline with nitrous acid, for example, gave the diazonium salt (**236**), which reacted with benzene to give the biphenyl derivative (**237**) in 46% yield.¹⁸³ The aromatic amine precursors are usually obtained by hydrogenation of nitrobenzene derivatives (secs. 4.8.D, 4.8.F).¹⁸⁴



A related process that involves diazonium salts is the **Pschorr reaction**,¹⁸⁵ which also couples aryl diazonium compounds to other aromatic rings. This diazonium salt coupling can be done under acidic conditions, but addition of copper powder usually promotes the radical process. Aryl amines generate aryl diazonium salts upon treatment with nitrous acid.¹⁸⁶ An example is the reaction of **238** to give an aryl diazonium salt, which cyclized in the presence of copper to give thaliporphine (**239**) in 43% yield. Kupchan called this transformation an improved Pschorr reaction.¹⁸⁷

^{180.} Citterio, A.; Cominelli, A.; Bonavoglia, F. Synthesis 1986, 308.

^{181. (}a) Ridd, J.H. Quart. Rev. Chem. Soc. 1961, 15, 418; (b) Hegarty, A.F. The Chemistry of Diazonium and Diazo Groups, Part 2, Patai, S. (Ed.), Wiley, New York, 1978, pp 511-591.

^{182. (}a) Bachmann, W.E.; Hoffman, R.A. Org. React. 1944, 2, 224 (see pp 225-226); (b) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-37.

^{183.} Gomberg, M.; Bachmann, W.E. J. Am. Chem. Soc. 1924, 46, 2339.

^{184.} Rylander, P.N. Catalytic Hydrogenation Over Platinum Metal, Academic Press, New York, 1967, pp 168-202.

^{185. (}a) Pschorr, R. Berichte 1896, 29, 496; (b) Leake, P.H. Chem. Rev. 1956, 56, 27; (c) DeTar, D.F. Org. React. 1957, 9, 409 (see pp 411-416); (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-76; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 534-535.

^{186. (}a) Kametani, T.; Fukumoto, K.; Satoh, F.; Yagi, H. J. Chem. Soc. Chem. Commun. 1968, 1398; (b) Idem. J. Chem. Soc. C. 1969, 520; (c) Kametani, T.; Ihara, M.; Fukumoto, K.; Yagi, H. Ibid. 1969, 2030.

^{187.} Kupchan, S.M.; Kameswaran, V.; Findlay, J.W.A. J. Org. Chem. 1973, 38, 405.



The **Ullmann reaction**,^{188,189} is very similar in that aryl halides are coupled to form biaryls (such as biphenyl) by heating with copper. Once again, the copper generates an aryl radical (in this case 16), which reacts with Cu⁺ to form an arylcopper(I) species (240). Subsequent reaction of the aryl copper with iodobenzene leads to a coupling reaction that gives biphenyl, which is related to the organocuprate coupling reactions discussed in Section 8.7.A.ii. The reaction is placed here because of the radical intermediate. This reaction is similar to the Ni(0) coupling reactions discussed in Section 12.8.^{190,191}



A halide reactivity depends on the halide: $I > Br > Cl.^{189}$ An electronegative group in the ortho position activates the reaction. Nitro groups on the aromatic ring are activating in this type of coupling:¹⁹² ortho > para > meta. 2-Iodonitrobenzene is very reactive, but the 3-iodo and 4-iodo derivatives are about as reactive as iodobenzene. Aromatic rings containing substituents are readily coupled using copper or copper salts.¹⁸⁹ In a synthesis of (+)-isokotanin A,¹⁹³ Bringmann and co-workers coupled aryl bromide **241** with copper in DMF to give symmetrical biaryl **242** in 89% yield. Functionalized aryls such as ferrocene can be coupled using copper salts,¹⁹⁴



⁽a) Ullmann, F.; Meyer, G.M.; Loewenthal, O.; Gilli, E. Annalen 1904, 332, 38; (b) Ullmann, F.; Sponagel, P. Berichte 1905, 38, 2211; (c) Fanta, P.E. Chem. Rev. 1946, 38, 139; (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-96; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 662-663.

- 189. Fanta, P.E. Chem. Rev. 1964, 64, 613.
- 190. Semmelhack, M.; Helquist, P.; Jones, L.D.; Keller, L.; Mendelson, L.; Ryono, L.S.; Smith, J.G.; Stauffer, R.D. J. Am. Chem. Soc. 1981, 103, 6460.
- 191. See Tsou, T.T.; Kochi, J.K. J. Am. Chem. Soc. 1979, 101, 7547.
- 192. Davey, W.; Latter, R.W. J. Chem. Soc. 1948, 264.
- 193. Bringmann, G.; Hinrichs, J.; Henschel, P.; Kraus, J.; Peters, K.; Peters, E.-M. Eur. J. Org. Chem. 2002, 1096.
- 194. Rausch, M.D. J. Org. Chem. 1961, 26, 1802.

For unsymmetrical coupling (two different aryl halides) the best yields are observed when one aryl halide is very reactive and the other is relatively unreactive. Reactive aryl halides have electronegative groups, such as nitro or carbomethoxy, ortho to the halogen. Aryl bromides and chlorides are best for unsymmetrical coupling, while iodo compounds tend to give symmetrical coupling (Ar–Ar rather than Ar–Ar').¹⁹⁵ Unreactive halides lack an ortho electronegative group and are usually iodo derivatives. When unsymmetrical coupling is attempted with two unreactive aryls, three biaryls are usually produced in approximately equal amounts.¹⁸⁹ Ultrasound is effective for the synthesis of diaryl ethers via the Ullmann reaction.¹⁹⁶

The disconnections for copper promoted coupling are



Alkynes can be coupled under a variety of conditions,¹⁹⁷ including reactions that involve alkynyl copper derivatives. There are two classical alkyne coupling reactions. The first is the **Glaser reaction**¹⁹⁸ in which an alkyne such as phenylacetylene reacts with basic cupric chloride (CuCl₂) to give a diyne (1,4-diphenyl-1,3-butadiyne) in 90% yield upon oxidation with air. The mechanism of this reaction has been studied, and Cu (II) has been proposed as an oxidant in the reaction.¹⁹⁹ It has been shown that molecular oxygen forms adducts with Cu(I) supported by tertiary amines²⁰⁰ which might be the intermediates, and mechanistic considerations²⁰¹ for this variation have also been reported. Note the similarity to the Sonogashira coupling using a palladium catalyst in section 12.7.D. The coupling can be done both inter- and intramolecularly.²⁰² An example of the latter is the coupling of the two terminal alkyne units in **243** to give diyne **244** (65% yield), in Myers and co-worker's²⁰³ synthesis of kedarcidin. This

^{195.} Forrest, J. J. Chem. Soc. 1960, 566, 574, 581, 589, 592, 594.

^{196.} Smith, K.; Jones, D. J. Chem. Soc. Perkin Trans. 1 1992, 407.

^{197.} Cadiot, P.; Chodkiewicz, W. in *Chemistry of Acetylenes*, Viehe, H.G. (Ed.), Marcel-Dekker, New York, 1969, pp 597-648.

^{198. (}a) Glaser, C. Berichte 1869, 2, 422; (b) Idem Annalen 1870, 154, 137. For a recent review, see (c) Siemsen, P.; Livingston, R.C.; Diederich, F. Angew. Chem. Int. Ed. 2000, 39, 2632; (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-37; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 276-277.

^{199.} Bohlmann, F.; Schoenowsky, H.; Inhoffen, E.; Grau, G. Chem. Ber. 1964, 97, 794.

^{200.} Wieghardt, K.; Chaudhury, P. Prog. Inorg. Chem. 1988, 35, 329.

^{201.} Fomina, L.; Vazquez, B.; Tkatchouk, E.; Fomine, S. Tetrahedron 2002, 58, 6741.

^{202.} For an example taken from a synthesis of the kedarcidin core structure, see Myers, A.G.; Goldberg, S.D. *Angew. Chem. Int. Ed.* 2000, 39, 2732.

^{203.} Myers, A.G.; Hogan, P.C.; Hurd, A.R.; Goldberg, S.D. Angew. Chem. Int. Ed, 2002, 41, 1062.

example clearly shows that the Glaser reaction is compatible with molecules bearing a vast array of functionality and stereochemistry. The second synthetic route is the **Cadiot-Chodkeiwicz coupling**,²⁰⁴ in which a bromoalkyne reacts with a terminal alkyne in the presence of copper derivatives and an amine to give a diyne. An example taken from Danishefsky and Yun's synthesis of panaxytriol,²⁰⁵ in which bromoalkyne **245** reacted with **246**, in the presence of CuCl, ethylamine, and hydroxylamine hydrochloride. Coupling gave diyne **247** (panaxytriol) in 63% yield. Glaser type coupling of alkynes can be accomplished with other copper derivatives, and with bases other than hydroxide. The mixture of cupric acetate and pyridine is an effective reagent for this coupling.²⁰⁶ It is also possible to couple alkynyl copper derivatives with aryl halides^{207,208} or other aromatic substrates.²⁰⁹ This methodology can also be applied in an Ullmann-type reaction, analogous to that described for aryl halides where a vinyl iodide is coupled in the presence of copper.²¹⁰ Alkynylsilanes can also be coupled using Cu(I) salts.²¹¹



The disconnections for copper promoted coupling of alkynes and alkenes are



- 204. (a) Chodkiewicz, W.; Cadiot, P. Compt. Rend. 1955, 241, 1055; (b) Chodkiewicz, W. Ann. Chim. 1957, 2, 819; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 128-129.
- 205. Yun, H.; Danishefsky, S.J. J. Org. Chem. 2003, 68, 4519.
- 206. Brown, A.B.; Whitlock, Jr., H.W. J. Am. Chem. Soc. 1989, 111, 3640.
- 207. (a) Posner, G.H. An Introduction to Synthesis Using Organocopper Reagents, Wiley, New York, **1980**, p 41; (b) House, H.O.; Umen, M.J. J. Org. Chem. **1973**, 38, 3893.
- 208. (a) Hatchard, W.R. J. Org. Chem. 1963, 28, 2163; (b) Stevens, R.D.; Castro, C.E. Ibid. 1963, 28, 3313.
- 209. (a) Bohlmann, F.; Kleine, K.-M.; Arndt, C. *Berichte* 1966, 99, 1642; (b) Bohlmann, F.; Bonnet, P.-H.; Hofmeister, H. *Ibid.* 1967, 100, 1200; (c) Bohlmann, F.; Zdero, C.; Gordon, W. *Ibid.* 1967, 100, 1193.
- 210. Cohen, T.; Poeth, T. J. Am. Chem. Soc. 1972, 94, 4363.
- 211. Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. J. Org. Chem. 2000, 65, 1780.

13.8.D Pinacol Coupling

A classical metal transfer reaction is the **pinacol reaction** or **pinacol coupling**,²¹² in which alkali metals react with a ketone such as 3-pentanone to produce a radical anion (ketyl **248**) via electron transfer (secs. 4.9.A, 4.9.B).²¹³ Other reagents developed that give pinacol coupling,²¹⁴ include samarium iodide,²¹⁵ titanium(IV) iodide²¹⁶ or TiCl₄-Bu₄NI²¹⁷ and lanthanide metals in the presence of chlorotrimethylsilane.²¹⁸ If a monovalent metal such as sodium or potassium is used in the presence of an alcohol (most commonly, ethanol), the carbonyl is reduced to the alcohol (sec. 4.9.B). If a bivalent metal such as magnesium is used, however, the ketyl is stabilized, and reduction is slow. Here, the ketyl behaves more like a radical, leading to the coupling product (**249**), hydrolysis of which leads to the diol **250**.^{212a,219} This reaction is a preferred method for the synthesis of 1,2-diols.^{219,220}



MOLECULAR MODELING: Radical Coupling

Radical coupling typically proceeds with little if any activation barrier, which means that is is under thermodynamic control. Consider recombination of α -(*tert*-butyl)benzyl radicals leading either to *meso* or *dl* forms of 2,2,5,5-tetramethyl-3,4-diphenylhexane.

Build the *meso* product as drawn, with the two phenyl groups in a *syn* planar arrangement. This will ensure that you get the *meso* form and not the d,l form. Obtain the energy. Then rotate the central bond

- 212. (a) Schreibman, A.A.P. Tetrahedron Lett. 1970, 4271; (b) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-74; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 512-513.
- For reactions of this type, see Larock, R.C., Comprehensive Organic Transformations, Wiley-VCH, New York, 1999, pp. 1111-1114.
- 214. Wirth, T. Angew. Chem. Int. Ed. 1996, 35, 61.
- 215. Ghatak, A.; Becker, F.F.; Banik, B.K. Tetrahedron Lett. 2000, 41, 3793.
- 216. Hayakawa, R.; Shimizu, M. Chem. Lett. 2000, 724.
- 217. Tsuritani, T.; Ito, S.; Shinokubo, H.; Oshima, K. J. Org. Chem. 2000, 65, 5066.
- 218. Ogawa, A.; Takeuchi, H.; Hirao, T. Tetrahedron Lett. 1999, 40, 7113.
- 219. Popp, F.D.; Schultz, H.P. Chem. Rev. 1962, 62, 19 (see pp 27-30).
- 220. Weber, J.E.; Boggs, A.D. J. Chem. Educ. 1952, 29, 363.

MOLECULAR MODELING: Radical Coupling, con't.

to generate the rotamer with the two phenyl groups *anti* planar. To rotate about a bond, first *click* on it and then move the mouse up and down while simultaneously holding down on the left button and the **Alt** key (**Option** key on Macintosh). Obtain its energy, and choose the better (lower-energy) conformer of the *meso* product. Next, build the *d*,*l* product, again starting with the two phenyl groups in a *syn* planar arrangement, and obtain its energy. Rotate into a conformation where the two phenyl groups are *anti*. Obtain the energy of this conformation and select the better (lower-energy) *d*,*l* product. Is the *meso* or *dl* form more stable? Assuming thermodynamic control, which diastereomer is predicted to be the major product?

An asymmetric pinacol coupling of aromatic aldehydes was reported by Enders and Ullrich, using TiCl₂ and an enantiopure amine or hydrazine reagent.²²¹ When benzaldehyde was treated with TiCl₂ and chiral amine $\begin{array}{c} & OH \\ & OH \\ & & OH \\ \hline \\ & & OMe \\ H \\ \textbf{251} \\ \textbf{251} \\ \hline \\ & & 251 \\ \hline \\ & & 251 \\ \hline \\ & & 252 \\ \hline \\ & & 0H \\ \hline \\ & & Ph \\ \hline \\ & & Ph \\ \textbf{252} \\ \hline \\ & & \textbf{252} \\ OH \\ \hline \end{array}$

251, a 31% yield of **252** was obtained as an 81:19 mixture of dl/meso diastereomers, and the *dl*-diastereomer was obtained in 65% ee (*S*,*S*).²²⁰ When the reaction time was increased to 48 hours, the yield improved to near quantitative but the diastereomeric ratio was 56:44 dl/meso and the enantioselectivity was only 37% ee.

$$\bigcirc H = 0 \xrightarrow{\text{Mg}^\circ, \text{ EtOH}} (1 + 1) \xrightarrow{\text{OH}} (1 + 1)$$

The preferred method for reductive coupling uses a mixture of magnesium and magnesium iodide, although the amalgam (Mg/Hg) can also be used.²²² A classical example is reductive condensation of cyclopentanone to the 1,2-glycol **253**.^{212a} 2,3-Dimethyl-2,3-butanediol (pinacol) is formed by reduction of acetone and gives the reaction its name.^{212a,220,219} Many other reductants can be used. Samarium iodide (SmI₂), mentioned above, was used for the coupling of benzaldehyde to **252** in 95% yield. Ytterbium as the free metal, has been used for the reduction of ketones but extensive coupling was observed. The extent of coupling depended on the ratio of ytterbium to ketone.²²³ A related ketyl coupling reaction is Molander and co-worker's conversion of **254** to the samarium stabilized ketyl **255**. Conjugate radical addition to the acrylate moiety gave **256**, and hydrolysis led to an 88% yield of **257** (200:1 diastereoselectivity).²²⁴ A catalytic and enantioselective pinacol coupling was reported that used chiral titanium (III) complexes, where the chiral ligand was a salen compound.²²⁵

^{221.} Enders, D.; Ullrich, E.C. Tetrahedron: Asymmetry 2000, 11, 3861.

^{222.} Adams, R.; Adams, E.W. Org. Synth. Coll. Vol. 1 1941, 459.

^{223.} Hou, Z.; Takamine, K.; Aoki, D.; Shiraishi, H.; Fujiwara, U.; Taniguchi, H. J. Org. Chem. 1988, 53, 6077.

^{224. (}a) Molander, G.A.; Kenny, C. J. Am. Chem. Soc. 1989, 111, 8236; (b) Molander, G.A.; Etter, J.B.; Zinke, P.W. Ibid. 1987, 109, 453.

^{225.} Chatterjee, A.; Bennur, T.H.; Joshi, N.N. J. Org. Chem. 2003, 68, 5668.


The pinacol coupling reaction can be applied to most ketones and aldehydes when two identical molecules are being coupled. An improvement in the reaction involves trapping the initial coupling product as the bis(trimethylsilyl) derivative. Coupling of 4'-methylacetophenone (**258**) with zinc²²⁶ in the presence of chlorotrimethylsilane gave 76% of the bis(*O*-silyl)ether **259**. Treatment with tetrabutylammonium fluoride removed the silyl protecting group (sec. 7.3.A.i) to give the pinacol product **260**. Coupling of two different ketones may lead to several different products in relative proportions close to those expected from statistical coupling. One product may predominate but the yields can be low. When cyclopentanone was coupled to cycloheptanone in the presence of aluminum and mercuric chloride (HgCl₂), for example, only 23% of the cross-coupled diol (**261**) was formed.²²⁷



The pinacol disconnection is:

$$R_2C(OH)-C(OH)R_2 \implies R_2C=O$$

Photoreductive coupling of aldimines leads to the synthesis of C_2 -symmetrical diamines. An example is the photocoupling of aldimine **262** to a 52:48 mixture of **263/264** in 85% yield.²²⁸



^{226.} So, J.-H.; Park, M.-K.; Boudjou, P. J. Org. Chem. 1988, 53, 5871.

^{227. (}a) Sands, R.D. Tetrahedron, 1965, 21, 887; (b) Sands, R.D.; Botteron, D.G. J. Org. Chem. 1963, 28, 2690.

^{228.} Campos, P.J.; Arranz, J.; Rodríguez, M.A. Tetrahedron 2000, 56, 7285.

13.8.E. The Acyloin Condensation



A variation of the pinacol reaction has been applied to esters for the preparation of α -hydroxy ketones (acyloins). A simple example is the reaction of 265 with sodium metal (Na^{\circ}) in refluxing xylene,²²⁹ which gave a good yield of 2-hydroxycycloheptanone (266) after hydrolysis. Bouveault and Loquin reported the condensation of a α,ω -diester to a α -hydroxy ketone,²³⁰ the acyloin condensation,^{231,229} in 1905.²³² The reaction works well with relatively high molecular weight esters in an intermolecular reaction. Methyl laurate (267), for example, was treated with Na° (in xylene at 110°C) to give a 90% yield of lauroin (268).²³³ The reaction conditions shown are typical, where high dilution techniques (sec. 6.6.B) were not required but effective stirring (high speed stirrer at 2000-2500 rpm) was necessary. The reaction proceeded²³⁴ via initial transfer of an electron to form a ketyl (269), which is in equilibrium with the coupling product (270) and the diketone (271). Transfer of a second electron to this mixture led to 272, and protonation generated a dihydroxy intermediate (273), which gave acyloin 273. Radical coupling of the ketyl intermediate is most efficient when the ketyl is bound to, or closely associated with the surface of the metal. The high-speed stirrer generates a fine "sodium sand", which maximizes the surface area for effective electron transfer and radical coupling of the ketyl. Under these conditions, both intermolecular coupling and intramolecular cyclization reactions are possible as shown in Table 13.4 for the conversion of diesters 275 to cyclic acyloins 276. The preparation of **269** is one example of an intermolecular acyloin condensation.

 ⁽a) McElvain, S.M. Org. React 1948, 4, 256; (b) Finley, K.T. Chem. Rev. 1964, 64, 573; (c) House, H.O. Modern Synthetic Reactions, 2nd Ed. W.A. Benjamin, Menlo Park, CA., 1972, pp 169-172.

^{230.} For transformations of this type, see reference 213, pp 1313-1315.

 ⁽a) Bloomfield, J.J.; Owsley, D.C.; Nelke, J.M. Org. React. 1976, 23, 259; (b) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-1; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 4-5.

^{232.} Bouveault, L.; Loquin, R. Compt. Rend. 1905, 140, 1593.

^{233. (}a) Hansley, V.L. J. Am. Chem. Soc. 1935, 57, 2303; (b) Ruzicka, L.; Plattner, Pl.A.; Widmer, W. Helv. Chim. Acta 1942, 25, 604, 1086.

^{234.} Reference 229a, pp 257 and 259.



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		x ^{(CI}	$(H_2)_m - CH_2CC$ $(H_2)_n - CH_2CO$ 275	$D_2 Me = \frac{1. N}{2. H}$	$I_{3}O^{+}$ X ≤ 0	(CH ₂) _n (CH ₂) _n 27	n 76	_≠ 0 `ОН	
X	<u>m</u>	<u>n</u>	<u>Ring Size</u>	<u>% 276</u>	X	<u>m</u>	<u>n</u>	Ring Size	<u>% 276</u>
CH ₂	2	1	8	47 ^c	cis- CH=CH	2	2	10	80 ^c
	2	2	9	9 ^b	trans- CH=CH	2	2	10	51 ^c
	2	3	10	45 ^b	Ph–N	1	1	7	10 ^c
	3	4	12	76 ^{a,b}		2	2	9	3°
	4	4 ^a	13	72 ^c	Me-N	2	2	9	75 ^c
	4	5 ^a	14	79 ^b		3	3	11	64 ^c
	5	5 ^a	15	77 ^b	Et–N	3	3	11	85 ^c
	5	6 ^a	16	84 ^b	C ₆ H ₁₁ -N	2	2	9	50 ^c
	6	6 ^a	17	85 ^b	<i>p</i> -Me-Ph-N	2	2	9	38 ^c
l	6	7 ^a	18	96 ^b	1,4-C ₆ H ₄	6	6	20	$0^{\rm c}$
	7	8 ^a	20	96 ^b		5	5	18	70 ^c
l	13	14 ^a	34	20 ^c		4	4	16	76 ^c
MeCH	2	2	9	60 ^c		3	4	15	36 ^c
C≡C	3	3	12	73 ^c		2	5	15	0^{c}
l	3	4	11	0^{c}		1	6	15	75 ^c
					^a diethyl ester, ^b l	Ref. 2	29a, ^c	² Ref. 229b.	
[Reprinted with permission from Finley, K.T. Chem. Rev. 1964, 64, 573. Copyright © 1964 American Chemical Society.]									

 Table 13.4
 Intramolecular Acyloin Condensations of 275

A modification of the acyloin condensation adds chlorotrimethylsilane to trap the alkoxide intermediate as a bis(silyl enol ether). This modification has become the standard version of the acyloin condensation. Rühlmann and co-workers showed that ethyl butanoate reacted with excess sodium to generate the expected bis(alkoxide) **277**. Addition of chlorotrimethylsilane

led to a 92% yield of the bis(trimethylsilyl)derivative, **278**,²³⁵ and hydrolysis with 1N HCl in THF gave 96% of the acyloin (**279**). This modification serves two purposes. First, trapping the enolate product allows its isolation and minimizes side reactions. Second, the *O*-TMS group protects the acyloin (see sec. 7.3.A.i), allowing further manipulation prior to unmasking the relatively sensitive α -hydroxyketone moiety. When there are no enolizable hydrogens in the *O*-TMS derivative, treatment with bromine generates a 1,2-diketone.²³⁶ When enolizable hydrogens are present the normal acyloin product is observed. A synthetic example is taken from Sih and co-worker's synthesis of castanospermine,²³⁷ in which diester **280** derived from hydroxy-proline was refluxed with sodium metal and chlorotrimethylsilane in toluene. This reaction led to formation of **281**, which could be isolated by chromatography, and converted to the corresponding acyloin by mild acid hydrolysis.



McMurry and Rico generated an acyloin-like reaction using a titanium trichloride (TiCl₃)– zinc-copper couple. α,ω -Dialdehydes are coupled with this reagent to give 1,2-diols.²³⁸ This procedure generates mixtures of cis and trans diols with the cis predominating for smaller rings and the trans predominating for larger rings.²³⁹ Cyclization of 1,6-hexanedial [OHC– (CH₂)₄–CHO] under these conditions gave only *cis*-1,2-cyclohexanediol in 85% yield, but cyclization of 1,12-dodecanedial [OHC–(CH₂)₁₀–CHO] gave a 25:75 cis/trans mixture of 1,2-cyclododecanediol²³⁹ in 75% yield. As with the acyloin condensation, good yields are realized even with medium size (8-13 membered) rings. An example, taken from Williams



and Heidebrecht's synthesis of (+)-4,5-deoxyneodolabelline,²³⁹ cyclized **282** with TiCl₃ and Zn/Cu (see Sect. 13.8.F) to give an 8:2:1:1 (*R*,*R*;*S*,*R*;*R*,*S*;*S*,*S*) mixture of **283** in 85% yield.

- 236. Strating, J.; Reiffers, S.; Wynberg, H. Synthesis 1971, 209.
- 237. Bhide, R.; Mortezaei, R.; Scilimati, A.; Sih, C.J. Tetrahedron Lett. 1990, 31, 4827.
- 238. McMurry, J.E.; Rico, J.G. Tetrahedron Lett. 1989, 30, 1169.
- 239. Williams, D.R.; Heidebrecht Jr., R.W. J. Am. Chem. Soc. 2003, 125, 1843.

 ⁽a) Schräpler, U.; Rühlmann, K. Chem. Ber. 1963, 96, 2780; (b) Rühlmann, K.; Poredda, S. J.Prakt. Chem. 1960, 12, 18.

The acyloin disconnections are



13.8.F McMurry Olefination

A useful relative of the acyloin condensation is the **McMurry olefination reaction**.²⁴⁰ In this reaction, ketones or aldehydes are treated with Ti(0) (TiCl₃ + LiAlH₄; TiCl₃ + K; TiCl₃ + Li)²⁴¹ to give alkenes.²⁴² Reductive coupling is possible with a wide variety of ketones and aldehydes.^{241a,243} Retinal (**284**), for example, was coupled with this reagent to give β -carotene (**285**) in 85% yield.²⁴³



The TiCl₃/K mixture is a commonly used reagent, and a variety of carbonyl compounds can be coupled to give the corresponding alkene.^{241a,244} Decanal was coupled with TiCl₃ and K to give a 60% yield of the C-20 alkene (10-icosene).²⁴⁴ Cross-coupling is also possible as illustrated by the treatment of a mixture of cycloheptanone and acetone with TiCl₃/Li to give a 50% yield of **286** along with 26% of **287**.²⁴⁴



The mechanistic studies of this coupling suggest it occurs "in a heterogeneous process on the surface of an active titanium particle", as outlined in Figure 13.7.²⁴² The byproduct is titanium dioxide (TiO₂) and electron transfer to the carbonyl generates the dianion (**288**), presumably via a ketyl-like intermediate. It has been suggested that the metallopinacol is not the only precursor, and that carbenoid intermediates and/or nucleophilic intermediates can be important.²⁴⁴ In the commonly accepted mechanism, the initially formed dianion binds to the

^{240. (}a) McMurry, J.E. Acc. Chem. Res. 1974, 7, 281; (b) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-58; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 416-417.

^{241.} McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. J. Org. Chem. 1978, 43, 3255.

^{242.} For transformations of this type, see reference 213, pp 305-308.

^{243.} McMurry, J.E.; Fleming, M.P. J. Am. Chem. Soc. 1974, 96, 4708.

^{244.} For discussions of the mechanism of this reaction, see (a) Stahl, M.; Pidun, U.; Frenking, G. Angew. Chem. Int. Ed. 1997, 36, 2234; (b) Villiers, C.; Ephritikhine, M. Angew. Chem. Int. Ed. 1997, 36, 2380.

titanium particle as shown, and sequential homolytic cleavage (via **289**) liberates the alkene and titanium dioxide. McMurry's experiments discredited alternative mechanisms such as formation of a discrete cyclic (or acyclic) titanium dialkoxy species.^{241a} This reagent also led to elimination of 1,2-diols to alkenes, as in the conversion of *trans*-1,2-cycloheptanediol to cycloheptene in 55%.^{245,241a}



Figure 13.7. Mechanism of the McMurry Coupling Reaction. [Reprinted with permission from McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. J. Org. Chem. **1978**, 43, 3255. Copyright © 1978 American Chemical Society.]

This reaction can be done intramolecularly and Zn–Cu/TiCl₃ is a common catalyst, although Zn and TiCl₄ are also used (see Table 13.5).²⁴² The final product of the intramolecular reaction is a cyclic alkene. Since the reaction proceeds via a titanium bound ketyl species, the two reactive ends are in close proximity, allowing efficient coupling of even medium and large rings analogous to the acyloin condensation.²⁴⁶ Table 13.5²⁴² shows the power of this reaction for the preparation of medium- and large-ring alkenes (**291**) from both diketones and dialdehydes (**290**). In a synthetic example, Corey and Hu converted diketone **292** to δ-araneosene (**293**) in 90% yield using McMurry coupling.²⁴⁷ It is noted that the McMurry coupling of esters leads to enol ethers.

Tuble 1010 Intrantolecular Mentally Coupling of Directories and Dialachyaes (2)

$(CH_2)_n \xrightarrow[]{II}_R R \xrightarrow{TiCl_3, Zn/Cu} (CH_2)_n \xrightarrow{R}_R$								
<u>n</u>	R	<u>R</u> ¹	% 291	<u>n</u>	R	<u>R</u> ¹	<u>% 291</u>	
2	Ph	Ph	87	10	Pr	Pr	71	
3	Ph	Me	70	11	Н	Н	52	
4	Me	C_7H_{15}	79	12	Н	Н	71	
6	Am	Am	67	12	Et	Et	75	
7	Am	Am	67	13	Н	Ph	80	
8	Bu	Bu	76	14	Н	Н	85	
9	Bu	Bu	76	20	Me	Me	83	
10	Н	Н	76					
[Reprinted with permission from McMurry, J.E.; Fleming, M.P.; Kees, K.L.; Krepski, L.R. J. Org. Chem. 1978, 43, 3255. Copyright © 1978 American Chemical Society.]								

^{245.} McMurry, J.E.; Fleming, M.P. J. Org. Chem. 1976, 41, 896.

^{246.} McMurry, J.E.; Kees, K.L J. Org. Chem. 1977, 42, 2655.

^{247.} Hu, T.; Corey, E.J. Org.Lett. 2002, 4, 2441.



The disconnections for McMurry coupling are



13.9 CARBENES AND CARBENOIDS

There is another class of molecules called carbenes, that in many ways can be considered to be *radical-like*. Carbenes have been known since the work of Curtius²⁴⁸ in the late 19th century and Staudinger²⁴⁹ in the early 20th century, and earlier work²⁵⁰ is known. Carbenes are important in several synthetic methods and are growing in importance, especially the intramolecular versions. *N*-Heterocyclic carbenes are important as universal ligands in organometallic and inorganic coordination chemistry.²⁵¹ "*N*-Heterocyclic carbenes both stabilize and activate metal centers in quite different key catalytic steps of organic syntheses".²⁵² The remaining sections of this chapter discuss the preparation and reactions of carbenes and related compounds.

13.9.A Definition of a Carbene

A carbene is a divalent carbon species linked to two adjacent groups by covalent bonds,²⁵²

possessing two nonbonded electrons and six valence electrons (as in **294**).²⁵³ The two nonbonded electrons can have anti-parallel spins in a single orbital (see **295**, a **singlet carbene**), or parallel spins in different orbitals (see **296**, a **triplet carbene**). Substituted carbenes (**297**)



are generated in the singlet state from most precursors, but "intersystem crossing to the triplet

^{248.} Buchner, E.; Curtius, T. Ber. Dtsch. Chem. Ges. 1885, 8, 2377.

^{249.} Staudinger, H.; Kupfer, O. Ber. Dtsch. Chem. Ges. 1912, 45, 501.

^{250.} Arduengo III, A.J.; Krafczyk, R. Chem. Unserer Zeit. 1998, 32, 6.

^{251.} Herrmann, W.A. Angew. Chem. Int. Ed. 2002, 41, 1291.

^{252.} For a discussion of stable carbenes, see Arduengo, III, A.J. Acc. Chem. Res. 1999, 32, 913.

 ⁽a) Kirmse, W. Carbene Chemistry, Academic Press, New York, 1971, pp 5-7; (b) Chinoporos, E. Chem. Rev. 1963, 63, 235; (c) Closs, G.L. Top. Stereochem. 1968, 3, 193; (d) Parham, W.E.; Schweizer, E.E. Org. React. 1964, 13, 55; (e) Brinker, U.H. (Ed.), Advances in Carbene Chemistry, Vol 1 and Vol. 2, Jai Press, Greenwich and Stamford, 1994 and 1998; (f) Regitz, M. Angew. Chem. Int. Ed. 1996, 35, 725.

(sec. 11.10.B) may or may not occur before the individual carbene reacts with a suitable precursor".²⁵⁴ "Singlet carbenes are electron deficient species comparable to carbocations," but "they possess a nonbonding pair of electrons comparable to that of carbanions."²⁵⁴ If an adjacent group on the carbene withdraws electrons, the carbene will have electrophilic character. If that group supplies electrons the carbene will have nucleophilic character. "Triplet carbenes may be considered as diradicals, although the interaction of two unpaired electrons in orbitals on the same carbon atom gives rise to some peculiarities."²⁵⁵ "The term carbenoid has been suggested" by Closs and Moss "for the description of intermediates which exhibit reactions qualitatively similar to those of carbenes without necessarily being free divalent carbon species".²⁵⁵ Although generally considered to reactive intermediates, stable carbenes are known, particularly persistent triplet diarylcarbenes and heteroatom-substituted singlet carbenes.²⁵⁶

13.9.B Preparation of Carbenes

There are several methods for the preparation of carbenes. A simple approach is to photolyze ketenes (**298**) at 270-370 nm (100.5-76.5 kcal mol⁻¹, 438.8-320.2 kJ mol⁻¹) in the presence of oxygen.²⁵⁷ Irradiation of **298** at 270 nm gave carbon monoxide (CO, with a quantum yield = 2) and the yield of ethene was independent of the pressure of oxygen. At 370 nm, the quantum yield of CO varies with the pressure of applied oxygen and also with the temperature. The presence of additional oxygen diminished the yield of ethene by $\approx \frac{2}{3}$.²²⁶ The reaction proceeded via formation of excited ketene (**299**), which fragments to methylene (**294**) and CO. The reactive carbene reacts with additional ketene to give ethene and CO. It was noted that a possible intermediate to **299** is an excited cyclopropanone species.²⁵⁸

$$\begin{array}{c} H \\ C = C = O \\ H \\ 298 \end{array} \xrightarrow{hv} \left[\begin{array}{c} H \\ C = C = O \\ H \\ 299 \end{array} \right]^{*} \longrightarrow \begin{array}{c} H \\ C : + C = O \\ H \\ 294 \end{array} \xrightarrow{H} \begin{array}{c} C : + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} 294 \\ CH_{2} = CH_{2} + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} CH_{2} = CH_{2} + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} CH_{2} = CH_{2} + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} CH_{2} = CH_{2} + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} CH_{2} = CH_{2} + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} CH_{2} = CH_{2} + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} CH_{2} = CH_{2} + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} CH_{2} = CH_{2} + CH_{2} = CH_{2} + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} CH_{2} = CH_{2} + CH_{2} + C = O \\ H \\ 299 \end{array} \xrightarrow{H} \begin{array}{c} CH_{2} = CH_{2} + CH_{2} +$$

Photolysis of alkyl and aryl ketenes generates alkyl and aryl carbenes. Methylketene and dimethylketene led to methylcarbene²⁵⁹ and dimethylcarbene,²⁶⁰ respectively, upon irradiation. The quantum yields were close to unity at 270 nm.²⁶¹ Methylcarbene coupled with itself to form an activated ethene, which gave both ethene and ethyne.²⁶⁰ 2-Butene was also formed by

^{254.} Reference 253a, p 5

^{255.} Reference 253a, p 6.

^{256.} Bourissou, D.; Guerret, O.; Gabbai, F.P.; Bertrand, G. Chem. Rev. 2000, 100, 39.

^{257.} Reference 253a, p 9.

^{258. (}a) Knox, K.; Norrish, R.G.W.; Porter, G. J. Chem. Soc. 1952, 1477; (b) Kistiakowsky, G.B.; Sauer, K. J. Am. Chem. Soc. 1956, 78, 5699; (c) Idem Ibid. 1958, 80, 1066.

^{259. (}a) Kistiakowsky, G.B.; Mahan, B.H. J. Am. Chem. Soc. 1957, 79, 2412; (b) Chong, D.P.; Kistiakowsky, G.B. J. Phys. Chem. 1964, 68, 1793.

^{260.} Halroyd, R.A.; Blacet, F.E. J. Am. Chem. Soc. 1957, 79, 4830.

^{261.} Reference 253a, p 14.

reaction with methyl carbene and the starting ketene. Similarly, photolysis of dimethylketene led to cyclopropanone (via dimethylcarbene and the ketene), which lost CO under the photolytic conditions to give 2,3-dimethyl-2-butene.²⁶¹

13.9.B.i. Diazomethane. Important precursors for the preparation of carbenes and related molecules are diazoalkanes. Although diazomethane is not used in carbene preparations, it has other synthetic applications, and is presented here for comparative purposes. There are four convenient preparations of diazomethane, which is a highly reactive gas. <u>Since diazomethane can detonate on contact with ground glass, its preparation requires the use of specialized glassware. Diazomethane is also toxic</u>.

All preparative methods for diazomethane (CH₂N₂) involve *N*-nitroso compounds. Treatment of commercially available *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald[®], **300**) with hydroxide liberates diazomethane and sulfonate ester **301**.²⁶² Similar treatment of *N*,*N'*dimethyl-*N*,*N'*-dinitrosoterephthalamide (**302**),²⁶³ *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG, **303**),²⁶⁴ or *N*-Methylnitrosourea (**304**)²⁶⁵ give diazomethane. It is noted that <u>MNNG *is allergenic and is potentially mutagenic*</u>. These reagents and synthetic uses of diazomethane are outlined in an excellent review by Hopps.²⁶⁶ It is noted that at least two other structural isomers of diazomethane are known, diazirine (**307**)²⁶⁷ and isodiazomethane (**308**).²⁶⁸



13.9.B.ii. Diazoalkanes. One of the most convenient and useful sources of reactive carbenes are diazoalkanes. Diazoalkanes (RN_2) have been known and used synthetically for over 50 years.²⁶⁹ The simplest diazoalkane is diazomethane, represented by several resonance hybrid structures (**309**), which are zwitterionic, although it can also be written as a nitrene. It is noted

266. Hopps,. H.B. Aldrichimica Acta 1970, 3, 9.

269. (a) Huisgen, R. Angew. Chem. 1955, 67, 439; (b) Cowell, G.W.; Ledwith, A. Quart. Rev. Chem. Soc. 1970, 24, 119.

^{262. (}a) de Boer, T.J.; Backer, H.J. Org. Synth., Coll. Vol. 4 1963, 250; (b) Idem Rec. Trav. Chim 1954, 73, 229.

^{263.} Moore, J.A.; Reed, D.E. Org. Synth. Coll. Vol. 5 1973, 351.

^{264. (}a) McKay, A.F. J. Am. Chem. Soc. 1948, 70, 1974; (b) McKay, A.F.; Ott, W.L.; Taylor, G.W.; Buchanan, M.N.; Crooker, J.F. Can. J. Res. 1950, 28B, 683.

^{265.} Arndt, F. Org. Synth. Coll. Vol. 2 1943, 165.

^{267. (}a) Schmitz, E. Angew. Chem. Int. Ed. 1964, 3, 333; (b) Idem Adv. Heterocyclic Chem. 1963, 2, 83 (see p 122); (c) Schmitz, E.; Ohme, R. Tetrahedron Lett. 1961, 612; (d) Paulsen, S.R. Angew. Chem. 1960, 72, 781.

^{268. (}a) Anselme, J.P. J. Chem. Educ. 1966, 43, 596; (b) Müller, E.; Ludsteck, D. Chem. Ber. 1954, 87, 1887.

that the chemistry of nitrenes is quite useful, particularly for generating aziridines, although we will not discuss it here.²⁷⁰ The preparation and reactions of other alkyl diazoalkanes are described in a review by Cowell.^{270b,271} Hydrazones (such as that from acetophenone, **310**) are convenient sources of carbenes via their reaction with *p*-toluenesulfonyl azide in THF to give the corresponding diazoalkane (311) along with *p*-toluenesulfonamide.²⁷²

$$\begin{bmatrix} H_2C = \overset{+}{N} = \overline{N} & \longleftrightarrow & H_2\overset{+}{C} - N = \overline{N} & \longleftrightarrow & H_2\overline{C} - N \equiv N & \longleftrightarrow & H_2\overline{C} - N \equiv N \\ 309 & 309 & & & \\ 309 & & & & \\ H_2\overline{C} - N \equiv N & & & \\ H_2\overline{C} - N \equiv N & & & \\ H_2\overline{C} - N \equiv N & & & \\ H_2\overline{C} - N \equiv N & \\ H_2\overline{C} - N \equiv N & & \\ H_2\overline{C} - N \equiv N & & \\ H_2\overline{C} - N \equiv N & \\ H_2\overline{C} - N = N & \\ H_2\overline{C} - N \equiv N & \\ H_2\overline{C} - N = N & \\ H_2\overline{C} - N = N & \\ H_2\overline{C} - N & \\ H_2\overline{C$$

The first aliphatic diazo compound known was ethyl diazoacetate (313), prepared by Curtius in 1883.²⁷³ Indeed, several types of amines can be converted to diazo compounds by treatment with potassium nitrite or nitrous acid. Treatment of ethyl glycinate hydrochloride (312) with potassium nitrite (KNO₂) gave **313**. This technique is most useful when an electronwithdrawing group is adjacent to the amino group.

$$EtO_2CH_2NH_2 \bullet HC1 \xrightarrow{KNO_2} EtO_2CCH=N_2 + KC1 + 2 H_2O$$
312
313

Photolysis of diazo compounds (314) generates nitrogen and the carbene 297. Photolysis of diazomethane (**314**, R = H), for example, generated methylene (H₂C:).²⁷⁴ Benzophenone is

$$R_2CN_2 \equiv \overset{R}{\underset{R}{\succ}} \overset{+}{\underset{314}{\times}} N^- \xrightarrow{hv} N_2 + \overset{..}{\underset{297}{\times}} R$$

often added as a sensitizer. Under these conditions, triplet methylene is formed via intersystem crossing $(S_1 \rightarrow T_1)^{275}$ (sec. 11.10.B). Energy transfer from triplet benzophenone to triplet diazomethane followed, and triplet diazomethane decomposed

to triplet methylene.²⁷⁶ A similar thermal reaction gives a carbene that reacts normally.²⁷⁷

Diazoalkanes (314) can undergo valence isomerization to Diazoalkanes (**314**) can undergo valence isomerization to diazirines (**315**) upon photolysis, but reversal to the diazoalkane occurs both photochemically and thermally.^{278,268cd} Diazirines $\stackrel{R}{\longrightarrow} \stackrel{h=}{\longrightarrow} \stackrel{n=}{\longrightarrow} \stackrel{n}{\longrightarrow} \stackrel{n$ occurs both photochemically and thermally.^{278,268cd} Diazirines

- 273. Curtius, T. Chem. Ber. 1883, 16, 2230.
- 274. Herzberg, G.; Shoosmith, J. Nature (London) 1959, 183, 1801.
- 275. (a) Bäckström, H.L.J.; Sandros, K. Acta Chem. Scand. 1958, 12, 823; (b) Idem Ibid. 1960, 14, 48; (c) Hammond, G.S.; Moore, W.M. J. Am. Chem. Soc. 1959, 81, 6334.
- 276. (a) Kopecky, K.R.; Hammond, G.S.; Leermakers, P.A. J. Am. Chem. Soc. 1961, 83, 2397; (b) Idem Ibid. **1962**, 84, 1015.
- 277. Staudinger, H.; Kupfer, O. Berichte 1912, 45, 501.
- 278. (a) Schmitz, E.; Oehme, R. Angew. Chem. 1961, 73, 115; (b) Idem Chem. Ber. 1961, 94, 2166.

^{270.} Müller, P.; Fruit, C. Chem. Rev. 2003, 103, 2905.

^{271. (}a) Jones, W.M.; Muck, D.L. J. Am. Chem. Soc. 1966, 88, 3798; (b) Jones, W.M.; Muck, D.L.; Tandy Jr., T.K. Ibid. 1966, 88, 68; (c) Applequist, D.E.; McGreer, D.E. Ibid. 1960, 82, 1965.

^{272.} Fischer, W.; Anselme, J.P. Tetrahedron Lett. 1968, 877.

can be photolyzed back to the diazoalkane or directly to the carbene.²⁷⁹

The diazoalkane disconnections are



13.9.B.iii. α -Diazocarbonyl Compounds. Another reaction that generates carbenes is a rearrangement of α -diazocarbonyl compounds (called the Wolff rearrangement),²⁸⁰ in which a diazocarbonyl compound (**316**) loses nitrogen (N₂) to give an acyl carbene (**317**). This reaction occurs under both thermal and photochemical conditions, and the resulting carbene rearranges to a ketene (**318**) (completing the Wolff rearrangement of diazoketone to ketene). In this case, the Wolff rearrangement to ketene **318** was followed by an internal [2+2]-cycloaddition (secs. 11.10.A, 11.10.C) to give **319** in 79% yield.²⁸¹ It is noted that hydrolysis of a ketene will generate an acid (or an ester in the presence of an alcohol).²⁸² Meinwald and Gassman used this rearrangement to "shrink" bicyclic systems. Irradiation of **320** in water gave a 68% yield of **321** via initial formation of a carbene (see **322**), and rearrangement to the ketene, **323**.²⁸³ Hydrolysis gave the carboxylic acid.



Diazoketones such as **316** can be formed from acid chlorides by reaction with diazomethane. Subsequent treatment with aqueous Ag_2O leads to the Wolff rearrangement and formation of a carboxylic acid of one carbon more than the starting acid chloride. This sequence is known

 ⁽a) Frey, H.M. Pure Appl. Chem. 1964, 9, 527; (b) Idem. Advan. Photochem. 1966, 4, 225; (b) Overberger, C.G.; Anselme, J.P. Tetrahedron Lett. 1963, 1405.

^{280. (}a) Wolff, L. Annalen 1912, 394, 23; (b) Reference 253a, pp 475-492; (c) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-103; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 702-703.

^{281.} Yates, P.; Fallis, A.G. Tetrahedron Lett. 1968, 2493.

^{282.} Bergmann, E.D.; Hoffmann, E. J. Org. Chem. 1961, 26, 3555.

^{283.} Meinwald, J.; Gassman, P.G. J. Am. Chem. Soc. 1960, 82, 2857.

as the **Arndt-Eistert synthesis**²⁸⁴ and the ketene can be trapped as an ester or an amide. A synthetic example is taken from Panek and Zhang's synthesis of herboxidiene/GEX 1A,²⁸⁵ in which ester **324** was saponified and then reacted with (*1*) oxalyl chloride, (*2*) CH₂N₂ to give a 97% yield of diazoketone **325**. Subsequent reaction with silver benzoate and pseudoephedrine gave an 80% yield of **326** via reaction with the ketone formed by a Wolff rearrangement.



The disconnections pertinent to these α -diazocarbonyl compounds are



13.9.B.iv. Photolysis of Cyclopropanes. Photolysis of cyclopropane derivatives²⁸⁶ will generate a carbene via elimination of an alkene. Photolysis of 1,1-dimethylcyclopropane in the gas phase gave dimethylmethylene (Me₂C:) and ethene,²⁸⁷ and irradiation of 9,10-dihydro-9,10-methanophenanthrene (**327**) gave carbene and phenanthrene.²⁸⁸ Oxiranes can be photolyzed to carbenes as well.²⁸⁹

$$\underset{Me}{\overset{hv}{\longrightarrow}} Me_2C: + CH_2=CH_2 \qquad \qquad \underset{327}{\overset{hv}{\longrightarrow}} \underset{}{\overset{hv}{\longrightarrow}} + : CH_2$$

The cyclopropane-alkene disconnection is



⁽a) Arndt, F.; Eistert, B. Berichte 1935, 68, 200; (b) Bachmann, W.E.; Struve, W.S. Org. React. 1942, I, 38; (c) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-3; (d) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 44-45.

289. Reference 287, pp 318-331.

^{285.} Zhang, Y.; Panek, J.S. Org. Lett. 2007, 9, 3141.

^{286.} Griffen, G.W.; Bertoniere, N.R. in *Carbenes, Vol 1*, Jones Jr., M.; Moss, R.A. (Eds.), Wiley, New York, *1977*, pp 305-317.

^{287.} Dhingra, A.K.; Koob, R.D. J. Phys. Chem. 1970, 74, 4490.

^{288.} Richardson, D.B.; Durrett, L.H.; Martin Jr., J.M.; Putnam, W.E.; Slaymaker, S.C.; Dvoretzky, I. J. Am. Chem. Soc. 1965, 87, 2763.

13.9.B.v. The Bamford-Stevens Reaction. Aldehydes and ketones such as **328** can be converted to a tosylhydrazone (**329**) via reaction with tosylhydrazine. Subsequent treatment with base followed by heating results in the loss of *p*-toluenesulfinate to give the corresponding diazo compound (**330**), which generates a carbene by loss of nitrogen and forms an alkene. The formation of alkenes from tosyl hydrazones when they are treated with base is called the **Bamford-Stevens reaction**.^{290,291a} The carbene nature of the intermediate was detected by examination of camphor tosylhydrazone,²⁹¹ which on heating with hydroxide give a mixture of camphene and tricyclene. When the reaction was done in acidic alcohols such as ethylene glycol, camphene was the main product (via rearrangement). In aprotic solvents, the carbene insertion products observed (sec. 13.9.C.iii). A synthetic example of the Bamford-Stevens reaction is taken from a synthesis of (+)-lasonolide A by Shishido and co-workers in which ketone **331** was converted to the tosylhydrazone (**332**) in 97% yield, and subsequent treatment with base gave alkene **333** in 86% yield.²⁹²



Although this is *not* a carbene mechanism and involves extrusion of nitrogen via a carbanion, it is included here for comparison with the reactions just cited. Grieco et al. used this method to convert **334** to diene **335** (>98% yield) in a synthesis of (\pm)-ivangulin.²⁹³ When an organolithium is used as the base, the alkene-forming reaction is sometimes called the **Shapiro reaction**.^{294,297b} Two equivalents of organolithium are required, and the reaction generates the *less substituted* alkene. In Sha and co-worker's synthesis of (–)-pinguisenol, tosylhydrazone **336** (generated from the ketone by reaction with tosylhydrazone in 91% yield) was treated with butyllithium

^{290. (}a) Bamford, W.R.; Stevens, T.S. J. Chem. Soc. 1952, 4735; (b) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-4; (c) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 56-57.

⁽a) Bayless, J.H.; Friedman, L.; Cook, F.B.; Schechter, H. J. Am. Chem. Soc. 1968, 90, 531; (b) Davies, H.W.; Schwarz, M. J. Org. Chem. 1965, 30, 1242; (d) Powell, J.W.; Whiting, M.C. Tetrahedron 1959, 7, 305; (e) Clarke, P.; Whiting, M.C.; Papenmeier, G.; Reusch, W. J. Org. Chem. 1962, 27, 3356.

^{292.} Yoshimura, T.; Yakushiji, F.; Kondo, S.; Wu, X.; Shindo, M.; Shishido, K. Org. Lett. 2006, 8, 475.

^{293.} Grieco, P.A.; Oguri, T.; Wang, C.-L, J.; Williams, E. J. Org. Chem. 1977, 42, 4113.

^{294. (}a) Shapiro, R.H. Tetrahedron Lett. 1968, 345; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis 2nd Ed. Wiley, New York, 2005, pp 590-591.

and TMEDA to give a 66% yield of **337**.²⁹⁵ The Bamford-Stevens reaction generates the *more substituted* alkene.



The relative amount of base has a significant effect on the product distribution. When the tosyl hydrazone of pinacolone was treated with > 1.8 equivalents of *n*-butyllithium, 3,3-dimethyl-1-butene was formed. When only 1 equivalent of *n*-butyllithium was used, however, a 57% yield of 3,3-dimethyl-1-butene, 40% of 1,1,2-trimethylcyclopropane, and 3% of the rearranged alkene (2,3-dimethyl-1-butene) were isolated.²⁹⁶ The type of base employed is also important. The product distribution from the hydrazone of cyclopentanone, for example, gave a mixture of cyclopentene/(*E*)-2-pentene/(*Z*)-2-pentene.²⁹⁷ When sodium methoxide was used, a 2:84:14 mixture of these products was obtained whereas sodium hydride led to a 83:14:3 mixture and sodium amide a 60:35:3 mixture.²⁹⁸

The Bamford-Stevens disconnection is

$$\begin{array}{c} R \\ R^{1} = N_{2} \end{array} \xrightarrow{R} \begin{array}{c} R \\ R^{1} = 0 \end{array} \qquad R \xrightarrow{R} \begin{array}{c} R^{1} \end{array} \xrightarrow{R} \end{array}$$

13.9.B.vi. Photolysis of Carbonyls. Under certain conditions, carbonyl compounds can be photolyzed to diradicals, and these can rearrange to carbenes.²⁹⁸ Photolysis of cyclobutanone **328** generated diradical **329**, and in one pathway it eliminated to form an alkene (**341**), thereby generating ketene **340**. It decarbonylated to form cyclopropane **342** via an alternative pathway. Yet another pathway involved ring expansion to give carbene **343**, which reacted with methanol to give **344**.²⁹⁹ When $R = R^1 = H$, 48% of **340** and **341** was observed, with 8% of **344** and a trace of **342**.^{299a} When $R = R^1 = Me$, however, 68% of **344** was obtained, along with 13% of **340** + **341** and 11% of **342**.^{299a}

- 297. Kirmse, W.; von Bülow, B.G.; Schepp, H. J. L. Ann. Chem. 1966, 691, 41.
- 298. Reference 253a, pp 47-51.
- 299. (a) Turro, N.J.; Southam, R.M. Tetrahedron Lett. 1967, 545; (b) Morton, D.R.; Lee-Ruff, E.; Southam, R.M.; Turro, N.J. J. Am. Chem. Soc. 1970, 92, 4349.

^{295.} Sha, C.-K.; Liao, H.-W.; Cheng, P.-C.; Yen, S.-C. J. Org. Chem. 2003, 68, 8704.

^{296. (}a) Kaufman, G.; Cook, F.; Shechter, H.; Bayless, J.; Friedman, L. J. Am. Chem. Soc. 1967, 89, 5736; (b) Shapiro, R.H.; Heath, M.J. Ibid. 1967, 89, 5734.



The carbonyl disconnection is:



13.9.B.vii. Halocarbenes. Polyhalomethanes can be converted to halocarbenes via photolysis, thermolysis, or treatment with base. When cyclohexene was treated with a mixture of chloromethane and phenylsodium, methylene $(:CH_2)$ was formed, and it added

MeCl, PhNa hexadecane to the alkene gave norcarane (**345**), but in only 3.2% yield.³⁰⁰ Obviously, chloromethane is not the best source of carbenes. Polyhalomethanes give much better results, and the most common

method for generating halocarbenes is treatment of dihalomethanes and trihalomethanes with sodium metal or with another base.³⁰¹

Chloroform is a particularly useful carbene precursor. Reaction of chloroform with hydroxide begins with an acid-base reaction to generate the anion (Cl_3C :) and water. Loss of chloride ion generates dichlorocarbene (Cl_2C :). Geuther suggested this type of carbene in 1862.³⁰² Potassium *tert*-butoxide is the base most commonly used to generate dichlorocarbene, after

its initial introduction by von E. Doering and Hoffmann.³⁰³ A typical reaction is that of cyclohexene and chloroform with potassium *tert*-butoxide to give **346**. In general, reactions with



alkenes give dichlorocyclopropanes [dibromocyclopropanes with bromoform (CHBr₃) and diiodocyclopropanes with iodoform (CHI₃)]. Tri-*n*-butyltin hydride (Bu₃SnH) can be used to reduce the product dihalide to a monohalide (sec. 4.9.H).

^{300.} Friedman, L.; Berger, J.G. J. Am. Chem. Soc. 1960, 82, 5758.

^{301.} Reference 253a, pp 129-150.

^{302.} Geuther, A. Annalen 1862, 123, 121.

^{303.} von E. Doering, W.; Hoffmann, A.K. J. Am. Chem. Soc. 1954, 76, 6162.

MOLECULAR MODELING: Addition of Singlet Dichlorocarbene to Ethylene

The term *singlet* is used to describe a molecule in which all electrons are paired, while the term *triplet* is used to describe a molecule in which two of the electrons are unpaired. While the vast majority of organic molecules are singlets, divalent carbon compounds (carbenes) may also exist as triplets. Most notable, the parent compound methylene, CH_2 , is a triplet. The chemistry of singlet and triplet carbenes is quite different, allowing them to be easily distinguished. Triplet carbenes generally behave as radicals, whereas singlet carbenes are typically electrophiles in that they add to carbon-carbon double bonds. For example, : CCl_2 , adds to ethylene to give 1,1-dichlorocyclopropane.

$$H_2CCl_2 + H_2C=CH_2 \longrightarrow \bigcirc_{Cl}^{Cl}$$

The transition state for this reaction is shown, as well as the energy profile for the addition. Examine the energy profile and identify the transition state as the structure at the top of the profile. "Walk" forward and back through the individual structures using the **Step** keys or animate the sequence using the **Play** key (all are found at the bottom left of the screen). What happens to the two reactants as the product (1,2-dichlorocyclopropane) is approached?

Rationalize the geometry of the transition state and the motion of the two reactants by examining the HOMO and LUMO for singlet dichlorocarbene. *Click* on > and then select *Continue* (not *New*) from the screen to bring up the builder panel. Start with methylene chloride and delete both hydrogen atoms to get dichlorocarbene. Are the highest-energy pair of electrons associated with the σ or π system of dichlorocarbene? Will the next pair of electrons be added to σ or π system? Next, examine an electrostatic potential map for :CCl₂. Recall that this colors an electron density surface which gives to overall molecular size and shape (where a reagent can approach) with the value of the electrostatic potential (the energy of a point positive charge with the nuclei and electrons of a molecule). By convention, electron-rich regions on are "red", electron-deficient regions are "blue" and neutral regions are "green". Where are the most "available" electrons located? Where are additional electrons most easily accommodated? Are your conclusions based on the electrostatic potential map consistent with those based on the HOMO and LUMO? What would you expect is the best geometry for approach of the two reagents? What would be the final geometry?

Typical halocarbene disconnections are



13.9.C. Reactions of Diazomethane

As with other diazoalkanes, diazomethane reacts with alkenes to form cyclopropane derivatives (sec. 13.9.C.i).³⁰⁴ Reaction with aromatic derivatives leads to ring expansion to cycloheptatriene derivatives.³⁰⁵ Both of these reactions (addition to an alkene or arene insertion) involve generation of an intermediate carbene and addition to a π bond.

^{304.} Muck, D.L.; Wilson, E.R. J. Org. Chem. 1968, 33, 419.

^{305.} Müller, E.; Kessler, H.; Fricke, H.; Kiedaisch, W. Annalen 1964, 675, 63.

Both reactions will be discussed below. Many of the reactions of diazomethane tend to be ionic in nature and are, therefore, set aside from the other diazoalkane chemistry in this section. One of the most prevalent uses of diazomethane itself is for esterification of small quantities of acids, especially acids that are precious for one reason or another. The reaction proceeds in near quantitative yield, producing a single product, as in Vidari and co-worker's conversion of **347** to methyl ester **348** in 90% isolated yield³⁰⁶ in a synthesis of J₂ isoprostane. Note that the esterification reaction is faster than reaction with the C=C unit.



Diazoalkanes undergo [3+2]-cycloadditions in the presence of alkenes to give pyrazolines, as discussed in Section 11.11.E. Diazomethane reacts with α -methylacrylonitrile, for example, to give pyrazoline **349** in 76% yield.³⁰⁷ In another ionic reaction, diazomethane reacts with aldehydes to give methyl ketones,³⁰⁸ as in the conversion of benzaldehyde to acetophenone (97% yield), which is a useful reaction for extending carbon chains. Diazomethane also reacts with cyclic ketones to give ring-expanded ketones, along with epoxides as minor products. This method was used to prepare cycloheptanone from cyclohexanone in 65% yield by reaction with diazomethane, along with 15% of oxaspirooctane.^{309,263a}



Some of these specialized diazoalkane disconnections are



13.9.D Carbene Reactions of Diazoalkanes

Carbenes are relatively easy to generate and they have several synthetic uses. Diazoalkanes are converted to the corresponding carbene photolytically, and in the presence of copper derivatives

^{306.} Zanoni, G.; Porta, A.; Castronovo, F.; Vidari, G. J. Org. Chem. 2003, 68, 6005.

^{307.} Gotkis, D.; Cloke, J.B. J. Am. Chem. Soc. 1934, 56, 2710.

^{308. (}a) Schlotterbeck, F. Chem. Ber. 1907, 40, 479; (b) Gutsche, C.D. Org. React. 1954, 8, 364.

^{309. (}a) House, H.O.; Grubbs, E.J.; Cannon, W.F. J. Am. Chem. Soc. 1960, 82, 4099; (b) Cram, D.J.; Helgeson, R.C. Ibid. 1966, 88, 3515.

such as Cu(acac)₂. Dirhodium tetraacetate [Rh₂ (OAc)₄] was found to be a better catalyst in some cases, initiating reaction with electron deficient alkenes.³¹⁰ Metal carbenes are important in synthesis.³¹¹ Carbenes can undergo 1,2-hydrogen shifts to generate alkene products. When diazine **350** was photolyzed (355 nm, 103.7 kcal mol⁻¹, 433.9 kJ mol⁻¹), chlorocarbene **351** was formed. In the presence of 2,3-dimethyl-2-butene, a 73% yield of the cyclopropane product (**353**) was produced.³¹² In addition to **353**, alkene **352** was formed by a 1,2-hydrogen shift during the course of the reaction and was competitive with the addition. The energy barrier for this rearrangement was calculated to be about 6.4 ± 2 kcal mol⁻¹ (26.79 ± 8.37 kJ mol⁻¹) and proceeded at a rate of 4.9-6.7 x 10⁷ s⁻¹.^{312a} Although the addition reaction is usually faster, the 1,2-shift should be considered an important side reaction in many carbene reactions.



13.9.D.i. Addition to Alkenes. Perhaps the most common reaction of carbenes is their addition to alkenes to generate cyclopropanes,³¹³ as shown in the formation of **353** above. A generalized example is the preparation of **355** from carbene **297** and alkene **354**.³¹⁴ The carbenes can be generated by any of the methods discussed in Section 13.9. The addition is usually exothermic³¹⁵ (a typical value is 91 kcal mol⁻¹, 380.9 kJ mol⁻¹), with an activation energy of ≈ 64 kcal mol⁻¹ (267.9 kJ mol⁻¹). Reaction of *cis*-and *trans*-2-butene with diazomethane

(under photolytic conditions) showed that the yield of cyclopropanes increased with increasing pressure. Insertion (see sec. 13.9.D.iv) into allylic and vinyl bonds was competitive in many cases. The reaction is stereoselective for retention of the geometry of the starting alkene, when diazomethane is used.³¹⁶ For other methylene precursors, *trans*-1,2-dimethylcyclopropane is

- (a) Jackson, J.E.; Soundararajan, N.; White, W.; Liu, M.T.H.; Bonneau, R.; Platz, M.S. J. Am. Chem. Soc. 1989, 111, 6874; (b) LaVilla, J.A.; Goodman, J.L. Ibid. 1989, 111, 6877.
- 313. For transformations of this type, see reference 213, pp 135-152. Also see Lebel, H.; Marcoux, J.-F.; Molinaro, C.; Charette, A.B. *Chem. Rev.* 2003, 103, 977.
- (a) Reference 253a, chapter 8, pp 267-362; (b) Moss, R.A. in *Carbenes, Vol. 1*, Jones, Jr., M.; Moss, R.A. (Eds.), Wiley, New York, *1973*, pp 153-304.
- 315. Reference 253a, p 268.
- 316. (a) Reference 253a, p 271; (b) McKnight, C.; Lee, P.S.T.; Rowland, F.S. J. Am. Chem. Soc. 1967, 89, 6802; (c) Eder, T.W.; Carr, Jr., R.W. J. Phys. Chem. 1969, 73, 2074; (d) Ring, D.F.; Rabinovitch, B.S. Ibid. 1968, 72, 191; (e) Duncan, F.J.; Cvetanovic, R.J. J. Am. Chem. Soc. 1962, 84, 3593; (f) Montague, D.C.; Rowland, F.S. J. Phys. Chem. 1968, 72, 3705; (g) Frey, H.M. J. Am. Chem. Soc. 1960, 82, 5947.

^{310.} Aggarwal, V.K.; Smith, H.W.; Hynd, G.; Jones, R.V.; Fieldhouse, R.; Spey, S.E. J. Chem. Soc. Perkin Trans. 1 2000, 3267.

^{311.} Dörwald, F.Z. Metal Carbenes in Organic Synthesis, Wiley-VCH, New York, 1999.

favored for both *cis*- and *trans*-2-butene.³¹⁷ The ratio of cis to trans isomers is, however, dependent upon the wavelength of light used, and on the additive. The reaction was more stereoselective at higher pressures, and when long wavelengths of light were used.³¹⁷ Molecular oxygen appears to be the best additive, and irradiation at 313 nm (91.4 kcal mol⁻¹, 382.6 kJ mol⁻¹) is optimal for methylene generation from ketenes. The yield of cyclopropanes from 2-butene was 87% at 366 nm (78.1 kcal mol⁻¹ = 326.9 kJ mol⁻¹), but only 29% at 313 nm.^{317c} Oxygen scavenges triplet methylene, which gives diminished stereoselectivity relative to singlet methylene, although isomerization of the active intermediates is also a factor.³¹⁸

	Me	<u> </u>	H ₂ Me	$\frac{1}{56} Me^{+} Me^{\frac{1}{2}}$	<u>∕</u> 357 ^{′Me}		
Alkene Geometry cis-	$\begin{array}{c} \underline{\text{Diazo Compound}}\\ \mathrm{CH}_2\mathrm{N}_2\\ Ph & Me \\ N_2 \\ O \\ Ph & N_2\\ O \\ Ph & N_2\\ O \\ N_2 \\ Me \\ O \\ N_2\\ MeO_2C \\ MeO_2C \\ N_2 \end{array}$	<u>hv</u> direct sensitized direct sensitized sensitized sensitized sensitized	356:357 0:100 34:66 4:96 15:85 50:50 55:45 56:44 86:14 90:10	Alkene Geometry trans-	$\begin{array}{c} \underline{\text{Diazo Compound}}\\ O\\ Ph \\ \swarrow N_2\\ \swarrow Ph \\ \swarrow N_2\\ MeO_2C\\ HeO_2C\\ MeO_2C \\ \end{array}$	<u>hν</u> direct sensitized sensitized direct sensitized	356:357 73:27 74:26 86:14 90:10 86:14

Table 13.6 cis-trans Selectivity of 2-Butene with Various Diazo Compounds

When the reaction occurs in the liquid phase, which is more common, the reaction is stereoselective unless the carbene "has a readily accessible triplet state".³¹⁹ Photolysis of diazomethane in the presence of *cis*-2-butene, for example, gave *cis*-1,2-dimethylcyclopropane (**357**) with complete retention of configuration.³²⁰ Other diazoalkanes led to a mixture of **356** and **357**. A decrease in stereoselectivity was observed when triplet methylene was produced (by photolysis of diazomethane) in the presence of a large excess of perfluoropropane ($CF_3CF_2CF_3$).^{317d} Reaction of triplet methylene with a cis alkene (**358**) proceeds by a two-step mechanism. The initially generated diradical (**359**) is in rotational equilibrium with **360**. Both

^{317. (}a) Frey, H.M. Proc. Roy. Soc. Ser. A 1959, 250, 409; (b) Idem Ibid. 1959, 251, 575.

^{318.} Reference 253a, p 272.

^{319.} Reference 253a, p 275.

^{320. (}a) Skell, P.S.; Woodworth, R.C. J. Am. Chem. Soc. 1956, 78, 4496, 6427; (b) Idem Ibid. 1959, 81, 3383;
(c) von E. Doering, W.; LaFlamme, P. Ibid. 1956, 78, 5447.

triplet diradicals are slowly converted to singlet diradical **361** and **362**, which give the ciscyclopropane **363** and the trans-cyclopropane **364**.^{321,321}



Singlet carbenes are produced from singlet diradicals, and close with high selectivity. Bond rotation in the triplet diradical is faster than $T_1 \rightarrow S_1$ conversion or ring closure. Ring closure of the singlet radical is faster than bond rotation (an equilibrium between **361** and **362** and unfavorable relative to conversion to **359** or **364**). Table 13.6^{322,277} summarizes the reaction of various diazo compounds (and the carbenes they produce) with 2-butene. There was a decrease in stereoselectivity for the sensitized reaction in comparison with direct photolysis. The rate of carbene addition also varies with the type of alkene, as shown in Table 13.7.³²³

 Table 13.7
 Rate of Carbene Addition as a Function of Both Alkene and Carbene

Carbene Generation (Relative Rate)							
Alkene	<u>A</u>	<u>B</u>	<u>C</u>	D	E	F	<u>G</u>
R	0.89	0.66	0.56	0.90	0.011	0.045	
RR	0.79		1.10		0.15		0.25
RR	0.78		1.01		0.23		0.53
\bigcirc		1.00		1.00	0.13	0.27	
R R	1.0		1.0		1.0	1.0	1.0
$R \xrightarrow{R} R$ R	1.17	3.32	1.9	1.62	2.8	2.0	2.5
$R \xrightarrow{R} R$ $R \xrightarrow{R} R$	1.13	3.46		1.6	6.5	1.85	4.4
$A. \ CH_2=C=O, \ 260 \ nm. B. \ CH_2N_2, \ Cu(II.) \qquad C. \ PhCHN_2/hv. \qquad D. \ EtO_2C-CHN_2/CuSO_4.$							
E. CHCl ₃ /KOt-Bu. F. CHBr ₃ /KOt-Bu. G. $\frac{Ph}{Br} \underset{N}{\swarrow} \frac{N}{N}$, hv.							

- 321. Reference 253a, p 283.
- 322. (a) Reference 253a, p 279; (b) Moritani, I.; Yamamoto, Y.; Murahashi, S. *Tetrahedron Lett.* 1968, 5697; (c) Cowan, D.O.; Couch, M.M.; Kopecky, K.R.; Hammond, G.S. *J. Org. Chem.* 1964, 29, 1922; (d) Jones, Jr., M.; Ando, W. *J. Am. Chem. Soc.* 1968, 90, 2200; (e) Jones, Jr., M.; Ando, W.; Kulczycki Jr., A. *Tetrahedron Lett.* 1967, 1391.
- 323. Reference 253a, pp 294-297.

When more than one alkene moiety is present, there is the potential for formation of isomers via addition to one or both of the double bonds. In general, carbenes add to the more electronrich alkene. Reaction of **365** with dichlorocarbene (Cl₂C:) gave only **366**, but **367** gave an 80% yield of **368**, with 20% of **369**.³²⁴ Where it is appropriate, there seems to be a preference for trans double bonds, as seen in the reaction of methylene with *cis,trans,trans*-1,5,9-cyclodecatriene (**370**), which gave a 97:3 mixture of **371/372**.³²⁵ It is noted that the trans double bond may be more sterically accessible, and this can account for the stereochemical preference. Similar reaction with dichlorocarbene and also with the Simmons-Smith reagent (sec. 13.9.D) showed the same preference for reaction with the (*E*)-alkene (this preference ranged from 2:1 to 9:1).



A wide range of cyclopropane derivatives can be prepared by this carbene addition to alkenes.³²⁶ There is a general preference for the less congested exo product in reactions with cyclic alkenes. Initial addition of the carbene can be accompanied by rearrangement of the product, as

discussed in the previous section (see above).³²⁷ In many cases, however, the cyclopropanation proceeds without rearrangement.



Diazoalkanes add to alkenes give cyclopropane derivatives in the presence of transition metal reagents. An example is the reaction of diazoketone **373** in the presence of copper triflate to give **374** (in 95% yield and 71% ee with the correct chiral ligand), taken from Nakada and co-workers' synthesis of (–)-methyl jasmonate.³²⁸

- 326. Reference 253a, pp 304-320.
- 327. Reference 253a, pp 321-328.

^{324.} Sims, J.J.; Honwad, V.K. J. Org. Chem. 1969, 34, 496.

^{325. (}a) Nozaki, H.; Kawanisi, M.; Noyori, R. J. Org. Chem. 1965, 30, 2216; (b) Nozaki, H.; Katô, S.; Noyori, R. Can. J. Chem. 1966, 44, 1021; (c) Locke, J.M.; Duck, E.W. Chem. Ind. (London) 1965, 1727; (d) Mühlstädt, M.; Graefe, J. Chem. Ber. 1966, 99, 1192; (e) Idem Z. Chem. 1969, 9, 303 [Chem. Abstr. 71:90918y 1969].

^{328.} Takeda, H.; Watanabe, H.; Nakada, M. *Tetrahedron* 2006, 62, 8054. For a synthesis of communesin F which employed an intramolecular cyclopropanation of an indole derivative with a diazolactone see Yang, J.; Wu, H.; Shen, L.; Qin, Y. J. Am. Chem. Soc. 2007, 129, 13794.

Carbenes generated the more traditional way react similarly. In Trost and Oslob's synthesis of (–)-anatoxin,³²⁹ the alkene unit in **375** reacted with dibromocarbene, generated from bromoform and base, to give an 85% yield of **376** and **377** as a 3.5:1 mixture of exo and endo isomers. Carbenes react with enamines in the normal way, as seen in the reaction of **373** to give **374**. However, in some cases the reaction is accompanied by a ring expansion that generates ketones via rearrangement of the initially formed aminocyclopropane. The cyclopropane product can be very stable and is usually isolated as the major product. Dichlorocarbene reacted with 1-piperidinocyclopentene (**378**) (derived from piperidine and cyclopentanone, see sec. 9.6.A) to give **379**. Loss of chloride ion generated the conjugated iminium chloride (**380**), and hydrolysis gave **381**.³³⁰



The disconnections available from carbene additions are



13.9.D.ii. Addition to Aromatic Derivatives. Aromatic compounds also react with carbenes, but ring expansion usually follows the initial cyclopropanation. In a typical example, 2-methoxynaphthalene (**382**) reacted with dichlorocarbene to give **383** and subsequent ring expansion gave **384**.³³¹ This is a general reaction of enol ethers to give either unsaturated acetals or unsaturated carbonyl compounds.³³²



^{329.} Trost, B.M.; Oslob, J.D. J. Am. Chem. Soc. 1999, 121, 3057.

- 331. Parham, W.E.; Bolon, D.A.; Schweizer, E.E. J. Am. Chem. Soc. 1961, 83, 603.
- 332. (a) Buddrus, J.; Nerdel, F.; Hentschel, P.; Klamann, D. *Tetrahedron Lett.* **1966**, 5379; (b) Nerdel, F.; Buddrus, J.; Brodowski, W.; Hentschell, P.; Klamann, D.; Weyerstahl, P. *Annalen* **1968**, 710, 36.

 ⁽a) Wolinsky, J.; Chan, D.; Novak, R. Chem. Ind. (London) 1965, 720; (b) Ohno, M. Tetrahedron Lett. 1963, 1753.

Rearrangement or ring opening of the cyclopropane adducts derived from aromatic compounds are possible, depending on the carbene. Addition of carbene to benzene gave norcarane **385** (R = H) and cycloheptatriene (**386**, R = H) in equilibrium. With functionalized norcarane products, ring opening usually occurs to give the substituted benzene, **387** (R = R¹= CN, for example). Product **386** is favored when **385** is generated by reaction of benzene with diazomethane or ester carbenes such as :CHCO₂R.³³³ Photolysis of diazomethane in benzene, for example, gave a 4.8:1 mixture of cycloheptatriene and toluene.³³⁴ This reaction is not restricted to simple benzene derivatives, and other aromatic rings can participate. In synthetic studies directed toward the guanacastepenes by Trauner and co-workers,³³⁵ for example, diazo derivative **388** was treated with the rhodium catalyst to give **389** by cyclopropanation of the aromatic furan ring. Ring opening led to a 50% yield of **390** by ring expansion and formation of an enol that tautomerized to the aldehyde unit.



Other carbenes react similarly, and the reaction can be applied to much more sophisticated substrates. In a synthetic example taken from Feldman and coworker's synthesis of pareitropone, alkynyl-tin biaryl **391** was first converted to hypervalent iodine derivative **392**.³³⁶ Subsequent treatment with base led to a cyclization reaction that formed the six-membered nitrogen-containing ring, and a vinyl carbene (**393**). Carbene insertion to the phenyl ring and ring expansion in the expected manner led to formation of the seven-membered ring found in pareitropone, **394**, in 64% overall yield.³³⁷ The course of the reaction is dictated by the inherent stability of the final product.³³⁷

- 335. Hughes, C.C.; Kennedy-Smith, J.J.; Truaner, D. Org. Lett. 2003, 5, 4113.
- 336. Feldman, K.S.; Cutarelli, T.D.; Di Florio, R. J. Org. Chem. 2002, 67, 8528.

^{333.} Reference 253a, p 381.

^{334. (}a) von E. Doering, W.; Knox, L.H. J. Am. Chem. Soc. 1950, 72, 2305; (b) Meerwein, H.; Disselnkötter, H.; Rappen, F.; von Rintelen, H.; van de Vloed, H. Annalen, 1957, 604, 151; (c) Lemmon, R.M.; Strohmeier, W. J. Am. Chem. Soc. 1959, 81, 106; (d) Russell, G.A.; Hendry, D.G. J. Org. Chem. 1963, 28, 1933.

 ⁽a) Sonnenberg, J.; Winstein, S. J. Org. Chem. 1962, 27, 748; (b) Skell, P.S.; Sandler, S.R. J. Am. Chem. Soc. 1958, 80, 2024; (c) Gatlin, L.; Glick, R.E.; Skell, P.S. Tetrahedron 1965, 21, 1315.



The carbene ring expansion disconnection is



13.9.D.iii. Cyclization Reactions of α -Diazo Ketones. An attractive application of the cyclopropanation reaction is intramolecular trapping of carbenes to form bicyclic compounds, with a three-membered ring appended to another ring. We saw an example of this reaction previously in the conversion of **373** to **374**. When diazoalkanes are treated with transition metals in the presence of an alkene, particularly copper or rhodium derivatives, cyclopropanation occurs although the reactive intermediate may not be a free carbene. With rhodium compounds, in particular, a C=Rh unit is the reactive species rather than a free carbene. A synthetic example from Srikrishna and Dethe's synthesis of (–)-cucumin H³³⁸ treated acid chloride **395** with diazomethane to give diazoketone **396**. Subsequent reaction with Cu-CuSO₄ gave cyclopropane derivative **397** in >70% overall yield. The mixture just cited is not required, and heating with cupric sulfate or copper metal³³⁹ can also be used to initiate this cyclization, as in von E. Doering's synthesis of barbaralone (**398**) by heating **399** with copper.³⁴⁰



This carbene insertion reaction has been used in a variety of syntheses and coupled with other synthetic techniques. Taber et al. used carbene cyclopropanation in several syntheses,

^{338.} Srikrishna, A.; Dethe, D.H. Org. Lett. 2003, 5, 2295.

^{339.} Julia, S.; Linstrumelle, G. Bull. Soc. Chim. Fr. 1966, 3490.

^{340.} von E. Doering, W.; Ferrier, B.M.; Fossel, E.T.; Hartenstein, J.H.; Jones Jr., M.; Klumpp, G.; Rubin, R.M.; Saunders, M. *Tetrahedron* 1967, 23, 3943.

including a copper-catalyzed synthesis of (+)-isoneonepatelactone.³⁴¹ Other diazo-carbonyl compounds can be used. In a synthesis of (–)-spirotryprostatin B,³⁴² Carreira and Meyers reacted diazolactam **400** (prepared from isatin)³⁴³ with 1,3-pentadiene, in the presence of the rhodium catalyst, to give a 71% yield of cyclopropyl derivative **401**. In another example, the reaction of diazoketone **402** and rhodium octanoate [Rh₂(oct)₄] produced a 52% yield of **403**, along with 28% of **404**.³⁴⁴ These compounds were used in further synthetic transformations in Taber and co-worker's synthesis of the ethyl ester of the major urinary metabolite of prostaglandin E₂.



The intramolecular carbene addition disconnections are



13.9.D.iv. C-H Insertion Reactions of α -Diazo Ketones. Taber and co-workers showed that diazocarbonyls undergo C-H insertion reactions in the presence of rhodium acetate $[Rh_2(OAc)_4]$,^{345b,346} as illustrated in syntheses of (±)-pentalenolactone E methyl ester³⁴⁷ and α -cuparenone.³⁴⁸ Other rhodium catalysts can be used. Fukuyama and co-workers applied this reaction to a synthesis of (–)-ephedradine A (also known as orantine).³⁴⁹ When **405** was treated

- 341. Taber, D.F.; Amedio Jr., J.C.; Raman, K. J. Org. Chem. 1988, 53, 2984.
- 342. Meyers, C.; Carreira, E.M. Angew. Chem. Int. Ed. 2003, 42, 694.
- 343. Cava, M.P.; Little, R.L.; Napier, D.R. J. Am. Chem. Soc. 1957, 80, 2257.
- 344. Taber, D.F.; Teng, D. J. Org. Chem., 2002, 67, 1607.
- 345. (a) Wenkert, E.; Davis, L.L.; Mylari, B.L.; Solomon, M.F.; da Silva, R.R.; Shulman, S.; Warnet, R.J.; Ceccherelli, P.; Curini, M.; Pellicciari, R. J. Org. Chem. 1982, 47, 3242; (b) Taber, D.F.; Petty, E.H. Ibid. 1982, 47, 4808.
- 346. Taber, D.F.; Ruckle Jr., R.E. J. Am. Chem. Soc. 1986, 108, 7686.
- 347. Taber, D.F.; Schuchardt, J.L. J. Am. Chem. Soc. 1985, 107, 5289.
- 348. Taber, D.F.; Petty, E.H.; Raman, K. J. Am. Chem. Soc. 1985, 107, 196.
- 349. Kurosawa, W.; Kan, T.; Fukuyama, T. J. Am. Chem. Soc. 2003, 125, 8112.

with 0.3% of a chiral rhodium catalyst known as the **Davies catalyst**³⁵⁰ [Rh₂(*S*-DOSP)₂, see the structure of the chiral DOSP ligand in the reaction scheme], the *trans*-dihydrobenzofuran derivative **406** was obtained in 63% yield (the yield is for two steps: conversion of the ester precursor to the diazo compound followed by cyclization by reaction with the rhodium complex). Note that Doyle and co-workers³⁵¹ developed several important rhodium catalysts, including the **Doyle catalysts**,³⁵² that are widely used in cyclopropanation and C–H insertion reactions. In a different example with a different catalyst, taken from a synthesis of (–)-tetrodotoxin,³⁵³ Du Bois and Hinman used Rh₂(HNCOCPh₃)₄ to convert **407** to **408**.



The carbene C-H insertion disconnection is



There is an interesting variation of this reaction that involves intramolecular N–H insertion of α -diazocarbonyls. When diazoketone **409** was treated with cupric bis(acetylacetonate), for example, a 74% yield of azetidinone (**410**) was obtained.³⁵⁴ It was shown that competitive

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- 353. Hinman, A.; Du Bois, J. J. Am. Chem. Soc. 2003, 125, 11510.
- 354. Wang, J.; Hou, Y.; Wu, P. J. Chem. Soc. Perkin Trans. 1 1999, 2277.

^{350. (}a) Davies, H.M.L.; Hansen, T.; Churchill, M.R. J. Am. Chem. Soc. 2000, 122, 3063; (b) Davies, H.M.L.; Hansen, T. J. Am. Chem. Soc. 1997, 119, 9075. Also see (c) Davies, H.M.L. Aldrichimica Acta 1997, 30, 107.

^{351. (}a) Doyle, M.P. Pure & Appl. Chem. 1998, 70 1123 (b) Doyle, M.P.; Protopopova, M.N. Tetrahedron, 1998, 54 7919 (c) Martin, S.F.; Spaller, M.R.; Liras, L.; Hartman, B. J. Am. Chem. Soc. 1994, 116 4493 (d) Doyle, M.P.; Kalinin, A.V. J. Org. Chem. 1996, 61 2179 (e) Doyle, M.P.; Dyatkin, A.B.; Roos, G.H.P.; Cañas, F., Pierson, D.A.; van Basten, A.; Mueller, P.; Polleux, P. J. Am. Chem. Soc. 1994, 116 4507. Also see Doyle, M.P.; Hu, W.; Valenzuela, M.V. J. Org. Chem. 2002, 67, 2954 for a synthesis of (S)-(+)-imperanene using these catalysts.

intramolecular C–H insertion by the carbenoid was not a problem, illustrated by the presence of ten equivalents of styrene in the reaction. The styrene actually seemed to enhance the N–H insertion reaction.



13.9.E Carbenoids

This section involves a class of compounds called carbenoids, which are reactive intermediates that react similarly to a carbene, but carbenes are not formed. The most commonly used carbenoid

$$CH_{2}I_{2} \rightarrow I \xrightarrow{\Box} \left[\begin{array}{c} & \Box \\ & \Box \\ & 411 \end{array} \right] \rightarrow \left[\begin{array}{c} & \Box \\ & 412 \end{array} \right] \rightarrow \left[\begin{array}{c} & \Box \\ & 412 \end{array} \right] \rightarrow \left[\begin{array}{c} & \Box \\ & 345 \end{array} \right]$$

is generated by reaction of diiodomethane and a Zn/Cu couple. When the carbenoid formed in this manner adds to alkenes, it is called the **Simmons-Smith reaction**.³⁵⁵

A simple example is the conversion of cyclohexene to bicyclo[4.1.0]heptane (norcarane, **345**). Initial reaction of diiodomethane with zinc gave an iodozinc compound (**411**, see sec. 9.8.B for a brief discussion of organozinc compounds), which reacted with the alkene to give **412**. Loss of zinc iodide (ZnI₂) gave the cyclopropane $\begin{bmatrix} P & P \end{bmatrix} \begin{bmatrix} P & P \end{bmatrix} \begin{bmatrix} P & P \end{bmatrix}$

derivative (**345** in this case).³⁵⁶ A onestep mechanism has also been proposed that involves **413**,^{356a,357} and generates the



cyclopropane derivative. The iodomethylene zinc intermediate is represented as **414**,³⁵⁸ based in part on the structure of known organozinc compounds.³⁵⁹



[Reprinted with permission from Simmons, H.E.; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.* **1973**, 20, 1. Copyright © **1973** by John Wiley and Sons, Inc.]

- 355. (a) Simmons, H.E.; Smith, R.D. J. Am. Chem. Soc. 1958, 80, 5323; (b) Idem. Ibid. 1959, 81, 4256; (c) Denis, J.M.; Girard, J.M.; Conia, J.M. Synthesis 1972, 549; (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-87; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 600-601.
- 356. Sawada, S.; Inouye, Y. Bull. Chem. Soc. Jpn. 1969, 42, 2669.
- 357. (a) Wittig, G.; Schwarzenbach, K. Annalen 1961, 650, 1; (b) Simmons, H.E.; Blanchard, E.P.; Smith, R.D. J. Am. Chem. Soc, 1964, 86, 1347; (c) Wittig, G.; Wingler, F. Chem. Ber. 1964, 97, 2146; (d) Blanchard, E.-P.; Simmons, H.E. J. Am. Chem. Soc. 1964, 86, 1337.
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- 359. Shearer, H.M.M.; Spencer, C.B. J. Chem. Soc. Chem. Commun. 1966, 194.

As with carbenes, more highly substituted alkenes react somewhat faster than less substituted alkenes.^{357d} Even highly substituted alkenes such as **415** gave an 87% yield of the Simmons-Smith product (**416**).³⁶⁰ It is known that 1-substituted cyclic alkenes react faster than unsubstituted



alkenes.³⁶¹ 1-Methylcyclohexene (relative rate 21.4) and methylenecyclohexane (relative rate 3.84) both react faster than cyclohexene (relative rate 1.0). 1,2-Dimethylcyclohexene, however,

reacts slightly slower, with relative rate of 0.94. Cyclohexene (relative rate 1.0) reacts slower than cyclopentene (relative rate 1.60) or norbornene (relative rate 1.70).³⁶² In addition, 1-methylcyclopentene (relative rate 5.14) reacts faster than cyclopentene (relative rate 1.60).³⁶²

Preparation of the zinc is critical to good yields in the Simmons-Smith reaction. Both Zn-

Cu and Zn-Ag couples have been used with both iodine and lithium.³⁶² The zinc must be activated or the yield of cyclopropane product is poor. A useful development is the use of ultrasound to activate the zinc. Treatment of



(-)- α -pinene (417) with the usual Simmons-Smith reagent gave only 12% of 418.³⁶³ When the zinc was activated by ultrasound, however, a 67% yield of 418 was obtained.³⁶⁴

An example of the Simmons-smith cyclopropanation is taken from a synthesis of cascarillic acid by Piva and Salim in which **419** was converted to a 90:10 mixture of cyclopropanes **420**:421 in 72% yield.^{365a} Electron-rich alkenes such as vinyl ethers and silyl enol ethers usually react faster than other alkenes.^{365b-d}



There is a pronounced neighboring-group effect when a hydrogen-bonding oxygen is a substituent. The oxygen will "coordinate with the reagent, increasing the rate and control the stereochemistry of the addition."^{366,361a,b} Reaction of **423**, for example, gave **425** via coordination of the oxygen in **424**. In a synthetic example, Casares and Maldonado used this

- 361. (a) Reference 253a, p 299; (b) Rickborn, B.; Chan, J.H.H. *J. Org Chem.* **1967**, *32*, 3576; (c) Balenkova, E.S.; Kochnova, G.P.; Khromov, S.I. *Neftekhimiya* **1969**, *9*, 29 [*Chem. Abstr.* 70: 106025x, **1969**].
- 362. Rieke, R.D.; Li, P.T-J., Burns, T.P.; Uhm, S.T. J. Org. Chem. 1981, 46, 4323.
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- 365. (a) Salim, H.; Piva, O. *Tetrahedron Lett.* 2007, 48, 2059; (b) Ragauskas, A.J.; Stothers, J.B. Can. J. Chem. 1985, 63, 2969; (c) Hoyano, Y.; Patel, V.; Stothers, J.B. *Ibid.* 1980, 58, 2730; (d) Jurlina, J.L.; Patel, H.A.; Stothers, J.B. *Ibid.* 1984, 62, 1159.
- 366. (a) Reference 253a, p 95; (b) Winstein, S.; Sonnenberg, J. J. Am. Chem. Soc. 1961, 83, 3235; (c) Dauben, W.G.; Berezin, G.H. Ibid. 1963, 85, 468; (d) Chan, J.H.; Rickborn, B. Ibid. 1968, 90, 6406.

^{360.} Koch, S.D.; Kliss, R.M.; Lopiekes, D.V.; Wineman, R.J. J. Org. Chem. 1961, 26, 3122.

neighboring group effect to convert 426 to 427 in a synthesis of β -cuparenone.³⁶⁷



An alternative preparative method avoids the use of the Zn/Cu couple, using diethyl zinc (Et_2Zn) .³⁶⁸ An example is taken from the synthesis of solandelactones E and F, by White and co-workers.³⁶⁹ In this work, **428** was treated with diethylzinc and diiodomethane to give a 97% yield of **429**.



Asymmetric induction is possible in the Simmons-Smith reaction if a suitable auxiliary is used, or if the chirality is built in via a chiral template precursor (sec. 10.9). When **430** was prepared from diethyl tartrate, subsequent treatment with diethylzinc gave a 99% yield of **431**.³⁷⁰ Subsequent hydrolysis gave **432** (74% yield and 90% ee), which allowed Yamamoto to complete an asymmetric synthesis of 5,6-methanoleukotriene A₄. Imai et al. has also reported a chiral boronic acid auxiliary that leads to good enantioselectivity in the Simmons-Smith reaction.³⁷¹ The ability to produce the highly useful cyclopropane derivatives with good-to-excellent enantiomeric purity greatly enhances the utility of an already classical reaction.



 ^{367. (}a) Casares, A.; Maldonado, L.A. Synth. Commun. 1976, 6, 11; also see (b) Ando, M.; Sayama, S.; Takase, K. Chem. Lett. 1979, 191.

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- 369. White, J.D.; Martin, W. H.C.; Lincoln, C.; Yang, J. Org. Lett. 2007, 9, 3481.
- 370. (a) Arai, I.; Mori, A.; Yamamoto, H. J. Am. Chem. Soc. 1985, 107, 8254; (b) Mori, A.; Arai, I.; Yamamoto, H. Tetrahedron, 1986, 42, 6447; (c) Mash, E.A.; Nelson, K.A. Ibid. 1987, 43, 679; (d) Mash, E.A.; Nelson, K.A.Tetrahedron Lett. 1986, 27, 1441.
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The Simmons-Smith disconnection is



An interesting extension of reactivity that involves the Simmons-Smith reagent chain extends



carbonyl compounds, as reported by Zercher. In a simple example, ketoester **433** was treated with diethylzinc and diiodomethane followed by

iodine.³⁷² Destruction of excess iodine with sodium thiosulfate, and elimination with DBU (Sec 2.9.A) gave an 86% yield of **434**. This sequence is a carbene-mediated chain extension.

The carbene-mediated chain extension disconnection is



13.10 METATHESIS REACTIONS

In the presence of transition metal catalysts, two alkenes such as 2,3-dimethyl-2-butene and 2,3-diethyl-3-hexene react to form the original alkenes along with 3-ethyl-2-methyl-2-pentene. This reaction is an example of **metathesis** or **alkene metathesis** (or **olefin metathesis**),³⁷³ and an alkene³⁷⁴ is produced from an alkene or diene precursor. As implied in the reaction shown, a mixture of alkenes can be formed, but the reaction can be controlled in many cases, as will be seen below. The mechanism of this reaction is probably a chain mechanism that involves initial formation of a metal-carbene complex.³⁷⁵ The metal-carbene reacts with each alkene to form

^{372.} Ronsheim, M.D. Zercher, C.K. J. Org. Chem. 2003, 68, 4535.

^{373. (}a) Drăgut, n, V.; Balaban, A.T.; Dimonie, M. Olefin Metathesis and Ring-Opening Polymerization of Cycloolefins, Wiley, NY, 1985; (b) Ivin, K.J. Olefin Metathesis, Academic Press, NY, 1983; (c) Schrock, R.R. J. Organomet. Chem. 1986, 300, 249; (d) Grubbs, R.H. in Wilkinson Comprehensive Organometallic Chemistry, Vol. 8, Pergamon, Elmsford, NY, 1982, pp 499; (e) Grubbs, R.H. Prog. Inorg. Chem. 1978, 24, 1; (f) Calderon, N. Acc. Chem. Res. 1972, 5, 127; (g) Haines, R.J.; Leigh, G.J. Chem. Soc. Rev. 1975, 4, 155; (h) Bailey, G.C. Catal. Rev. 1969, 3, 37; (i) Grubbs, R.H. Tetrahedron 2004, 60, 7117; (j) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-67.

^{374.} For transformations of this type, see reference 213, p 401.

 ⁽a) Collman, J.C.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. Principles and Applications of Organotransition Metal Chemistry, 2nd Ed. University Science Books, Mill Valley, CA, 1987, pp 459-520; (b) Lindner, E. Adv. Heterocyclic Chem. 1986, 39, 237.

a four-membered ring containing a metal (**437** and **438** from **436**; **439** and **440** from **435**).³⁷⁶ Decomposition of the four-membered ring generates the two possible alkenes (2,3-dimethyl-2-butene and 3-ethyl-2-methyl-2-pentene from **440**, for example), and regenerates a metal carbene complex. The net result is formation of new alkenes. A single unsymmetrical alkene gives a mixture of itself and two other alkenes, and a mixture of two alkenes gives different alkenes, but the number depends on the symmetry of the reactants. The reaction can be done intermolecularly between two alkenes, or intramolecularly using dienes. Both intermolecular and intramolecular reactions of dienes are known.³⁷⁷ Simple alkenes usually give a statistical mixture of products,³⁷⁸ but thermodynamic stability can influence the relative proportion of products. The equilibrium can be shifted if one of the products is volatile, such as ethylene. Terminal and internal alkenes have been used and the facility of reaction changes with branching according to the order CH₂= > RCH₂CH= > R₂CHCH= > R₂C=.³⁷⁹



^{376.} For reviews of the mechanism, see (a) Grubbs, R.H. Prog. Inorg. Chem. 1978, 24, 1; (b) Calderon, N.; Ofstead, E.A.; Judy, W.A. Angew. Chem. Int. Ed. 1976, 15, 401; (c) McLain, S.J.; Wood, C.D.; Schrock, R.R. J. Am. Chem. Soc. 1977, 99, 3519; (d) Casey, C.P.; Polichnowski, S.W. J. Am. Chem. Soc. 1977, 99, 6097; (e) Mango, F.D. J. Am. Chem. Soc. 1977, 99, 6117; (f) Stevens, A.E.; Beauchamp, J.L. J. Am. Chem. Soc. 1979, 101, 6449; (g) Lee, J.B.; Ott, K.C.; Grubbs, R.H. J. Am. Chem. Soc. 1982, 104, 7491; (h) Kress, J.; Osborn, J.A.; Greene, R.M.E.; Ivin, K.J.; Rooney, J.J. J. Am. Chem. Soc. 1987, 109, 899; (g) Feldman, J.; Davis, W.M.; Schrock, R.R. Organometallics 1989, 8, 2266.

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^{377. (}a) Kroll, W.R.; Doyle, G. Chem. Commun. 1971, 839; (b) Grubbs, R.H.; Miller, S.J.; Fu, G.C. Acc. Chem. Res. 1995, 28, 446.



Metathesis reactions³⁸⁰ are well known, using both homogeneous³⁸¹ and heterogeneous³⁸² catalysts. Although other catalysts have been used,³⁸³ ruthenium complexes³⁸⁴ are the most common. With the development of the **Grubbs I catalyst** (441)³⁸⁵ and the **Schrock catalyst** (442),³⁸⁶ the reaction has taken on increased synthetic utility. The most common hes [ring-closing metathesis (RCM) reactions]

application is formation of cyclic alkenes [ring-closing metathesis (RCM) reactions].

The Grubbs catalyst is stable to Lewis acid conditions.³⁸⁷ Catalysts have been developed that allow the reaction to take place in aqueous and alcohol solution,³⁸⁸ and polymer-bound catalysts have been used.³⁸⁹ Microwave-assisted ring-closing metastasis reactions have also been reported.³⁹⁰ Note that there are some problems in handling the Grubbs' catalyst, in that prolonged exposure to air and moisture deactivates the complex. Therefore, the catalyst is usually stored under inert atmosphere. Attaching the active ruthenium complex to a polymer support improves the stability of the catalyst while retaining its reactivity in ring-closing metathesis.³⁹¹ Taber and Frankowski reported that Grubbs catalyst dispersed in paraffin is easily handled, and retains its activity indefinitely with no special storage precautions.³⁹²

Intramolecular metathesis reactions dominate synthetic applications, and alkenes containing

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- 386. (a) Bazan, G.C.; Oskam, J.H.; Cho, H.-N.; Park, L.Y.; Schrock, R.R. J. Am. Chem. Soc. 1991, 113, 6899, and references cited therein; (b) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, p. 845.
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- 390. (a) Mayo, K.G.; Nearhoof, E.H.; Kiddle, J.J. Org. Lett. 2002, 4, 1567; (b) Garbacia, S.; Desai, B.; Lavastre, O.; Kappe, C.O. J. Org. Chem. 2003, 68, 9136.
- (a) Dowden, J.; Savovic, J. *Chem. Commun.* 2001, 37; (b) Jafarpour, L.; Nolan, S.P. Org. Lett. 2000, 2, 4075;
 (c) Ahmed, M.; Barrett, A.G.M.; Braddock, D.C.; Cramp, S.M.; Procopiou, P.A. *Tetrahedron Lett.* 1999, 40, 8657. (d) Ahmed, M.; Arnauld, T.; Barrett, A.M.G.; Braddock, D.C.; Procopiou, P.A. Synlett 2000, 1007.
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^{380.} Grubbs, R.H.; Miller, S.J.; Fu, G.C. Acc. Chem. Res. 1995, 28, 446.

a =CH₂ unit are commonly used so that one product is ethylene. Ethylene escapes from the reaction medium and drives the equilibrium toward the cyclized product. A representative example is taken from the Kerr and Young synthesis³⁹³ of (+)-nakadomarin A, in which diene **443** was treated with 0.4 equivalents of **441** to give a 66% yield of the cyclized product **444** as a 5:3 mixture of *E:Z* isomers, along with the volatile ethylene.



With some of the early catalysts, alkenes containing functional groups³⁹⁴ did not work very well. This limitation prompted the development of alternative metathesis catalysts. In Leighton and co-worker's synthesis of dolabelide D,³⁹⁵ for example, the highly functionalized substrate **445** gave a 31% yield of **447** (dolabelide D) using **446** (the so-called **second generation Grubbs catalyst**, or **Grubbs II catalyst**, where Mes = mesitoate and Cy = cyclohexyl). Compounds with nitrogen in the ring being formed have also been prepared.³⁹⁶ An example is taken from Nishida and co-worker's synthesis of nakadomarin A,³⁹⁷ where the two vinyl units **448** were cyclized to form the eight-membered lactam ring in **449** using **446**³⁹⁸ Catalyst **446** is more stable and more active than **441**. There are now many synthetic examples that employ **446** rather than **441**. One of the more attractive features of this methodology is the ability to form macrocyclic compounds, as seen in the synthesis of **447**. The Schrock catalyst (**442**) also widely used. An example is taken from Nelson and co-worker's synthesis of (–)-laulimalide,³⁹⁹ in which **450** was converted to **451** in excellent yield. Other ruthenium catalysts are known, and in a variety of applications the metathesis reaction has been shown to proceed with good stereoselectivity.⁴⁰⁰

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- 400. Lee, C.W.; Grubbs, R.H. Org. Lett. 2000, 2, 2145.

^{393.} Young, I.S.; Kerr, M.A. J. Am. Chem. Soc. 2007, 129, 1465.

 ^{394. (}a) Mol, J.C. Chemtech 1983, 250-255; (b) Bosma, R.H.A.; van den Aardweg, G.C.N.; Mol, J.C. J. Organomet. Chem. 1983, 255, 159; (c) Idem Ibid. 1985, 280, 115; (d) Xiaoding, X.; Mol, J.C. J. Chem. Soc. Chem. Commun. 1985, 631; (e) Crisp, C.T.; Collis, M.P. Aust. J. Chem. 1988, 41, 935.

^{395.} Park, P.K.; O'Malley, S.J.; Schmidt, D.R.; Leighton, J.L. J. Am. Chem. Soc. 2006, 128, 2796.

^{398. (}a) Scholl, M.; Ding, S.; Lee, C.W.; Grubbs, R.H. Org. Lett. 1999, 1, 953. Also see (b) Love, J.A.; Sanford, M.S.; Day, M.W.; Grubbs, R.H. J. Am. Chem. Soc. 2003, 125, 10103.



As a synthetic method, cross metathesis reactions⁴⁰¹ have been limited by the lack of predictability of product selectively and stereoselectivity. Grubbs and co-workers have advanced a general model that is useful for predicting selectivity.⁴⁰² As stated by Grubbs, a general ranking of alkene reactivity is achieved by categorizing alkenes by their relative ability to undergo homodimerization via cross metathesis, and the susceptibility of their homodimers toward secondary metathesis reactions.⁴⁰² Suppressing the rate of homodimerization of one component and controlling the rate of secondary metathesis on the desired cross product gives product selectivity.⁴⁰² Grubbs provided a table (see Table 13.8) to assist ranking alkenes as to their reactivity.⁴⁰²

^{401.} Connon, S.J.; Blechert, S. Angew. Chem. Int. Ed. 2003, 42, 1900.

^{402.} Chatterjee, A.K.; Choi, T.-L.; Sanders, D.P.; Grubbs, R.H. J. Am. Chem. Soc. 2003, 125, 11360.

 Table 13.8
 Alkene categories for selective cross metathesis.⁴⁰²

Metathesis catalyst ⇒ <u>Alkene Type</u> (↓)	<u>446</u>	<u>441</u>	<u>442</u>				
Type I (fast homodimerization)	terminal alkenes, 1° allylic alcohols, esters, allyl boronate esters, allyl halides, styrenes (no large ortho substitutents), allyl silanes, allyl phosphontes, allyl sulfides, allyl phosphine oxides, protected allyl amines	terminal alkenes, allyl silanes, 1° allylic alcohols, ethers, esters, allyl boronate esters, allyl halides	terminal alkenes, allyl silanes				
Type II (slow homodimerization)	styrenes (large ortho substituents), acylates, acrylamides, acrylic acid, acrolein, vinyl ketones, unprotected, 3° allylic alcohols, vinyl epoxides, 2° allylic alcohols, perfluorinated alkanes, alkenes	styrene, 2° allylic alcohols, vinyl dioxolanes, vinyl boronates	styrene, allyl stannanes				
Type III (no homodimerization)	1,1-disubstituted alkenes, non-bulky trisubstituted alkenes, vinyl phosphonates, phenyl vinyl sulfone, 4° allylic carbons (all alkyl substitutents, 3° allylic alcohols (protected)	vinyl siloxanes	3° allyl amines, acrylonitrile				
Type IV (spectators to cross metathesis)	vinyl nitro alkenes trisubstituted allylic alcohols (protected)	1,1-disubstituted alkenes, disubstituted α,β-unsaturated carbonyls, 4° allylic carbon alkenes, perfluorinated alkanes, alkenes, 3° allyl amines (protected)	1,1-disubstituted alkenes				
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Metathesis with alkynes is also quite useful in synthesis,⁴⁰³ particularly for internal alkynes⁴⁰⁴ although terminal alkynes are not good partners in this reaction.⁴⁰⁵ Internal metathesis reactions with alkynes are known,⁴⁰⁶ including the conversion of **452** to **453** (in 73% yield) in Fürstner's synthesis of prostaglandin E_2 -1,15-lactone.⁴⁰⁷ Note the use of a molybdenum metathesis catalyst for this reaction. Diynes also react with alkynes in an intermolecular reaction to form aromatic rings. An example is the conversion of **454** to a 6:1 mixture of **455/456** in 82% yield.^{408a} A similar, palladium-catalyzed cycloaromatization is also known.⁴⁰⁹ Shmidt and co-

^{403.} Bunz, U.H.F.; Kloppenburg, L. Angew. Chem. Int. Ed. 1999, 38, 478.

^{404. (}a) Pennella, F.; Banks, R.L.; Bailey, G.C. Chem. Commun. 1968, 1548; (b) Villemin, D.; Cadiot, P. Tetrahedron Lett. 1982, 23, 5139; (c) McCullough, L.G.; Schrock, R.R. J. Am. Chem. Soc. 1984, 106, 4067; (d) Tamao, K.; Kobayashi, K.; Ito, Y. Synlett 1992, 539.

^{405.} McCullough, L.G.; Listemann, M.L.; Schrock, R.R.; Churchill, M.R.; Ziller, J.W. J. Am. Chem. Soc. 1983, 105, 6729.

^{406. (}a) Trost, B.M.; Trost, M.K. J. Am. Chem. Soc. 1991, 113, 1850; (b) Gilbertson, S.R.; Hoge, G.S. Tetrahedron Lett. 1998, 39, 2075.

^{407.} Fürstner, A.; Grela, K. Angew. Chem. Int. Ed. 2000, 39, 1234.

^{408. (}a) Witulski, B.; Stengel, T.; Fernández-Hernández, J.M. Chem. Commun. 2000, 1965. Also see (b) Yamamoto, Y.; Ogawa, R.; Itoh, K. Chem. Commun. 2000, 549.

^{409.} Yamamoto, Y.; Nagata, A.; Itoh, K. Tetrahedron Lett. 1999, 40, 5035.

workers reported cautionary note,⁴¹⁰ in that difficult-to-cyclize substrates can have a radical cyclization process (see sec. 13.7) compete effectively. The first and second-generation (see below) catalysts exhibit different activities when competing with radical cyclization.



Grubbs and co-workers have reported another useful variation of the metathesis reaction, for the synthesis of macrocyclic compounds. When bis(conjugated) ketone **457** reacted with cyclooctene⁴¹¹ in the presence of **446**, metathesis led to the ring expanded diketone **458** in 45% yield.



The ring-closing metathesis disconnections are



Another important application of metathesis reactions is to break C=C bond to form dienes, in what is called **ring-opening metathesis** (ROM).⁴¹² Both the first and second-generation Grubbs' catalysts have been used, as well as other catalysts. This methodology has been

^{410.} Schmidt, B.; Pohler, M.; Costisella, B. J. Org. Chem. 2004, 69, 1421.

^{411.} Lee, C.W.; Choi, T.-L.; Grubbs, R.H. J. Am. Chem. Soc. 2002, 124, 3224.

^{412. (}a) Bespalova, N.B.; Bovina, M.A.; Sergeeva, M.B.; Oppengeim, V.D.; Zaikin, V.G. J. Mol. Catal. 1994, 90, 21; (b) Zuercher, W.J.; Scholl, M.; Grubbs, R.H. J. Org. Chem. 1998, 63, 4291; (c) Randl, S.; Connon, S.J.; Blechert, S. Chem. Commun. 2001, 1796; (d) Morgan, J.P.; Morrill, C.; Grubbs, R.H. Org. Lett. 2002, 4, 67.
used extensively in polymerization reactions called ring-opening metathesis polymerization (ROMP),⁴¹³ but only recently in total synthesis. An example of ring opening metathesis in this latter context is taken from a synthesis of F2-isoprostanes, Snapper and co-worker reacted **459** with **446** to give a 67% yield of **460**,⁴¹⁴ as a 1.4:1 mixture of *Z:E* isomers.



The ring-opening metathesis disconnection is:

$$(CH_2)_n \qquad (CH_2)_n$$

The synthetic importance of ring-closing and ring-opening metathesis reactions has led to the development of several new catalysts.⁴¹⁵ Air stability, reactivity, robust character and improved reactivity are the goals of such new catalysts. A sample of newer catalysts includes **461** by Hoveyda,⁴¹⁶ **462** by Grela,⁴¹⁷ **463** by Blechert,⁴¹⁸ and **464** by Moore.⁴¹⁹ The latter catalyst (**464**) was particularly useful for the metathesis homocoupling of alkynes. Hoveyda, Schrock and co-workers developed a polymer-supported, recyclable molybdenum catalyst.⁴²⁰



^{413. (}a) Novak, B.M.; Grubbs, R.H. Encycl. Polym. Sci. Eng. 1990, Suppl. Vol. 420; (b) Amass, A.J. New Methods Polym. Synth. 1991, 76; Grubbs, R.H.; Khosravi, E. Materials Science and Technology 1999, 20 (Synthesis of Polymers) 65.

- 414. Schrader, T.O.; Snapper, M.L. J. Am. Chem. Soc. 2002, 124, 10998.
- 415. Schrock, R.R.; Hoveyda, A.H. Angew. Chem. Int. Ed. 2003. 42, 4592.
- (a) Kingsbury, J.S.; Harrity, J.P.A.; Bonitatebus, P.J.; Hoveyda, A.H. J. Am. Chem. Soc. 1999, 121, 791; (b) Garber, S.B.; Kingsbury, J.S.; Gray, B.L.; Hoveyda, A.H. Ibid, 2000, 122, 8168.
- 417. (a) Grela, K.; Kim, M. Eur. J. Org. Chem. 2003, 963; (b) Grela, K.; Harutyunyan, S.; Michrowska, A. Angew. Chem. Int. Ed. 2002, 41, 4038.
- 418. (a) Wakamatsu, H.; Blechert, S. Angew. Chem. Int. Ed. 2002, 41, 794; (b) Conon, S.J.; Dunne, A.M.; Blechert, S. Angew. Chem. Int. Ed. 2002, 41, 3835.
- 419. Zhang, W.; Kraft, S.; Moore, J.S. J. Am. Chem. Soc. 2004, 126, 329.
- 420. Hutlzsch, K.C.; Jernelius, J.A.; Hoveyda, A.H.; Schrock, R.R. Angew. Chem. Int. Ed. 2002, 41, 589.

13.11 PAUSON-KHAND REACTION

An interesting cyclization reaction was reported that involved the reaction of dienes, diynes or ene-ynes with transition metals to form cyclopentenone derivatives in the presence of carbon



monoxide.⁴²¹ In a simple example, ene-yne **465** was heated with dicobalt octacarbonyl and CO to give a 68% yield of **466**.⁴²² This transformation has become an important synthetic tool

known as the **Pauson-Khand reaction**.⁴²³ The mechanism probably involves insertion of the alkene (or alkyne) into the transition metal bond, which is why it is presented in this section. Formally, it is a [2+2+1]-cycloaddition, but the accepted mechanism is the one proposed by Magnus,⁴²³ and shown in Figure 13.8.⁴²⁴ It has been stated that further study is required to firmly establish the mechanism⁴²⁵ although Krafft's work supports the one reported by Magnus.⁴²⁵ Recently, Gimbert and co-workers showed that CO is lost from the Pauson-Khand complex prior to alkene coordination and insertion.⁴²⁶ Milet, Gimbert and co-worker's performed calculations that concluded the LUMO of the coordinated alkene plays a crucial role in alkene reactivity, by largely determining the degree of back-donation in the complex.⁴²⁷ Formation of the C–C bond is strongly influenced by the effectiveness of the LUMO overlap with the HOMO of the Co₂(CO)_x-complex, and such overlap is impacted by the degree of back-donation.⁴²⁸ Other metal complexes have been used,⁴²⁸ and the addition of primary amines enhances the rate of the reaction.⁴²⁹ Aldehydes have been used as a source of CO in some cases.⁴³⁰ Gibson has reported the use of heptacarbonyl(triphenylphosphine)cobalt (0) as a robust, and stable Pauson-Khand catalyst.⁴³¹

425. Krafft, M.E. Tetrahedron Lett. 1988, 29, 999.

- 427. de Bruin, T.J.M.; Milet, A.; Greene, A.E.; Gimbert, Y. J. Org. Chem. 2004, 69, 1075.
- 428. (a) Koga, Y.; Kobayashi, T.; Narasaka, K. Chem. Lett. 1998, 249; (b) Hoye, T.R.; Suriano, J.A. J. Am. Chem. Soc. 1993, 115, 1154.
- 429. Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. Angew. Chem. Int. Ed. 1997, 36, 2801.

^{421.} For transformations of this type, see reference 213, pp 1369, 1371-1372.

^{422.} Magnus, P.; Principe, L.M. Tetrahedron Lett. 1985, 26, 4851.

^{423. (}a) Khand, I.U.; Knox, G.R.; Pauson, P.L.; Watts, W.E.; Foreman, M.I. J. Chem. Soc. Perkin Trans. 1 1973, 977; (b) Khand, I.U.; Pauson, P.L.; Habib, M.J. J. Chem. Res. (S) 1978, 348; (c) Khand, I.U; Pauson, P.L. J. Chem. Soc. Perkin Trans. 1 1976, 30; (d) The Merck Index, 14th Ed. Merck & Co., Inc., Whitehouse Station, New Jersey, 2006, p ONR-69; (e) Mundy, B.P.; Ellerd, M.G.; Favaloro Jr., F.G. Name Reactions and Reagents in Organic Synthesis, 2nd Ed. Wiley-Interscience, New Jersey, 2005, pp. 486-487.

^{424.} For a review, see Brummond, K.M.; Kent, J.L. Tetrahedron 2000, 56, 3263.

^{426.} Gimbert, Y.; Lesage, D.; Milet, A.; fournier, F.; Greene, A.E.; Tabet, J.-C. Org. Lett. 2003, 5, 4073.

^{430.} Shibata, T.; Toshida, N.; Takagi, K. Org. Lett. 2002, 4, 1619.

^{431.} Gibson, S.E.; Johnston, C.; Stevenazzi, A. Tetrahedron 2002, 58, 4937.



Figure 13.8. Magnus Mechanism for the Pauson-Khand Reaction. [Reprinted with the permission from Magnus, P.; Principe, L.M. *Tetrahedron Lett.* **1985**, *26*, 4851, Copyright 1985, with permission from Elsevier Science.]

This reaction has found its way into organic synthesis,⁴²⁵ and is attractive because of its generality and selectivity. In a synthetic study aimed at nitiol that prepared two 1,22-dihydroxynitianes,⁴³² Dake and co-workers used a Pauson-Khand reaction of the alkene-alkyne **467** to give an 86% yield of **468** and **469** as a 6.2:1 mixture of diastereomers. Very sophisticated ring systems can be produced by this technique. An example is Cook and co-worker's synthesis of [5.5.5.5]-tetracyclic systems (pentalenes) in which **470** was treated with Mo(CO)₆ to give an 89% yield of **471**.⁴³³



Although this reaction usually requires stoichiometric amounts of the metal carbonyl, Kraft and co-workers have shown that substoichiometric amounts can be used⁴³⁴ (35-50% of Co₂(CO)₈, nitrogen atmosphere, in dimethoxyethane with three equivalents of cyclohexylamine. The use of amines to promote the reaction was mentioned above. Kraft and Boñaga also developed dodecacarbonyltetracobalt as a viable catalyst,⁴³⁵ and catalytic Pauson-Khand reactions are

^{432.} Wilson, M.S.; Woo, J.C.S.; Dake, G.R. J. Org. Chem. 2006, 71, 4237.

^{433.} Cao, H.; Van Ornum, S.G.; Cook, J.M. Tetrahedron Lett. 2000, 41, 5313.

^{434.} Krafft, M.E.; Bañaga, L.V.R. Synlett, 2000, 959.

^{435.} Krafft, M.E.; Boñaga, L.V.R. Angew. Chem. Int. Ed. 2000, 39, 3676.

now well established.⁴³⁶ A more robust Pauson-Khand catalyst has been developed, heptac arbonyl(triphenylphosphine)dicobalt(0).⁴³⁷ Molecular sieves have been used to promote the Pauson-Khand reaction,⁴³⁷ and high intensity ultrasound is also effective.⁴³⁸ Polymer-supported promoters of this reaction are known.⁴³⁹ In the presence of rhodium catalysts under solvent-free conditions, aldehydes serve as a CO source.⁴⁴⁰ Manipulating the reaction conditions, the catalyst, solvent and the length of time allowed for the reaction can give bicyclooctanones, as well as the usual bicyclooctenone products.⁴⁴¹

Enantioselective versions of the Pauson-Khand reaction have been reported.⁴⁴² Brucine-*N*-oxide promotes an asymmetric Pauson-Khand reaction, for example.⁴⁴³ An enantiospecific variation⁴⁴⁴ has been reported by using a menthol chiral auxiliary and by replacing one of the cobalt centers with an isoelectronic molybdenum fragment. Chiral phosphine derivatives have also proven to be effective,⁴⁴⁵ as have catalytic amounts of chiral aryl biphosphites.⁴⁴⁶ An aza-Pauson-Khand reaction was used in a synthesis of physostigmine by Mukai and co-workers,⁴⁴⁷ the reaction of alkyne-diimide **472** and the cobalt catalyst gave a 55% yield of **473** with a pyrrolo[2,3-*b*]-indol-2-one unit.



The Pauson-Khand disconnection is



^{436. (}a) Gibson, S.E.; Johnstone, C.; Stevenazzi, A. *Tetrahedron* 2002, 58, 4937; (b) Gibson, S.E.; Stevenazzi, A., *Angew. Chem. Int. Ed.* 2003, 42, 1800.

- 437. Pérez-Serrano, L.; Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. J. Org. Chem. 2000, 65, 3513.
- 438. Ford, J.G.; Kerr, W.J.; Kirk, G.G.; Lindsay, D.M.; Middlemiss, D. Synlett 2000, 1415.
- 439. (a) Kerr, W.J.; Lindsay, D.M.; McLaughlin, M.; Pauson, P.L. *Chem. Commun.* 2000, 1467; (b) Brown, D.S.; Campbell, E.; Kerr, W.J.; Lindsay, D.M.; Morrison, A.J.; Pike, K.G.; Watson, S.P. *Synlett*, 2000, 1573.
 440. Clineter, T. T.L. L. N., T.L. S. K., C. (7, 744).
- 440. Shibata, T.; Tshida, N.; Takagi, K. J. Org. Chem. 2002, 67, 7446.
- 441. Krafft, M.E.; Boñaga, L.V.R.; Wright, J.A.; Hirosawa, C. J. Org. Chem. 2002, 67, 1233.
- 442. Ingate, S.T.; Marco-Contelles, J. Org. Prep. Proceed. Int. 1998, 30, 121.
- 443. Kerr, W.J.; Lindsay, D.M.; Rankin, E.M.; Scott, J.S.; Watson, S.P. Tetrahedron Lett. 2000, 41, 3229.
- 444. Fletcher, A.J.; Rutherford, D.T.; Christie, S.D.R. Synlett 2000, 1040.
- 445. Verdaguer, X.; Moyano, A.; Pericàs, M.A.; Riera, A.; Maestro, M.A.; Mahía, J. J. Am. Chem. Soc. 2000, 122, 10242.
- 446. Sturla, S.J.; Buchwald, S.L. J. Org. Chem. 2002, 67, 3398.
- 447. Mukai, C.; Yoshida, T.; Sorimachi, M.; Odani, A. Org. Lett. 2006, 8, 83.

13.12 CONCLUSION

This chapter has shown the great control and selectivity of modern radical reactions, especially intramolecular radical coupling reactions. Carbenes, especially those derived from diazoalkenes, have also played a prominent role in organic synthesis. The chemical reactions illustrated in this chapter are excellent additions to the list of nucleophilic, pericyclic, and electrophilic reactions presented previously. This chapter concludes the methodology for generating carbon-carbon bonds. With the functional group reactions in the first part of the book, all the tools for pursuing a synthesis are at hand.

The last chapter will present several actual syntheses done by students, not their teachers. Examination of these syntheses will show common mistakes made by beginning synthetic chemists. They will also show some of the correct approaches to presenting a synthesis.

HOMEWORK

1. Predict the major product of the following reaction and briefly discuss why it is formed and other possible products are not (or are minor products).



2. Treatment of this molecule with mercury produced a radical. This radical product literally sat on the shelf for 25 years before the work was published. Give the structure of the radical and discuss its stability.



3. The structure of Fremy's salt is given. It is a rather stable free radical. Discuss the stability of this salt and also discuss its synthetic utility.

4. The two products of this reaction show stereochemical variation in the five-membered ring. Explain why the relative stereochemistry of the methyl group and two ring-juncture hydrogen atoms are the same in both products.



5. Explain the following results.



6. Explain the following rate data for the reaction shown.

R (relative rate): Ph- (17.0); n-BuO- (3.9); MeO₂C- (2.0); n-C₆H₁₃- (1.0); ClCH₂- (0.7).

$$R \underbrace{HS}_{(CH_2)_{10}} CH_3 \xrightarrow{R} S_{(CH_2)_{10}} CH_3$$

7. Why is benzophenone added to the following reaction? Give a mechanistic rationale for this transformation.



8. Give the mechanism for this transformation.



9. Explain the formation of the indicated product from β -pinene and carbon tetrachloride.



10. Explain the following transformation:



11. Explain the following transformation:



12. Two major cyclized products are produced in this reaction. Draw their structures and discuss the mechanism of their formation.



13. Explain the following transformation:



14. Three products are formed in this reaction, two minor and one major. Show all three products and indicate which one is the major product. Explain your choice.



15. Explain the following transformation.



16. In each case show the major product. Indicate stereochemistry where appropriate.







17. In each case provide a suitable synthesis from the designated starting material. Show all intermediate products and all reagents.















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chapter 14 Student Synthesis: The First Synthetic Problem

14.1 INTRODUCTION

It is one thing to learn all the reactions and processes described in this book. It is another to apply them to a complex molecule. A total synthesis first demands a review and understanding of the various disconnections and retrosynthesis strategies. Once a strategy is chosen, functional group exchange reactions best suited to a particular strategy. Reactions pertinent to the problem are then studied, which should force a thorough literature search (in the library or using one of the various literature searching techniques available for computers). Every step forces a complete review of chemical principles, stereochemical and conformational relationships in order to justify the use of each reagent that is not obvious. This collection of steps must then be examined for continuity, and the continuum of functional groups must all be compatible. In other words, groups introduced in the first synthetic step must not react with any succeeding steps. If they do, protection of those groups or redesign of the strategy is required. This discussion clearly suggests that a total synthesis focuses attention on organic chemistry in a way few, if any, other area of organic chemistry is able to do. For these reasons, a synthesis and reactions course often includes a proposal by the student for the synthesis of a natural product.

In most of the papers where a total synthesis is presented, the strategy and rationale for the synthesis is given. Most of the paper is devoted to explaining how and why the reactions worked, the stereochemical and conformational importance of various steps and, in some cases, a detailed explanation of things that did not work well in the initial planning. If a detailed study of published syntheses is of interest, and it should be to anyone proposing to synthesize a molecule, there is an excellent series that will provide information about how and why a synthesis was done. Lindberg's excellent series "Strategies and Tactics in Organic Synthesis", Volumes 1–3 [QD 262.s85] (1984, 1989, and 1991), Academic Press, San Diego is *strongly* suggested for anyone who is using this book in a synthesis course.

The course that spawned this book asked the students to prepare a synthesis proposal. There are many formats for the write-up, including those used by the National Institutes of Health (NIH) and the National Science Foundation (NSF). Each have somewhat different formats and page requirements. It is convenient to write a synthesis proposal following one of these formats, although any arbitrary format is acceptable. Proposals are submitted electronically to

both organizations, but adherence to the older format will suffice for our purposes.



This chapter is intended to show the first synthesis submitted by students who have had a course based on the material in this book. Scanning the literature will provide many examples of finished and polished total syntheses. Many have been used as source material to illustrate various reactions and those literature citations will lead to a broader explanation of that particular synthesis. The work behind such publications, however, is sometimes lost in the highly focused final paper. Various attempts to solve problems are sometimes, but not

always fully discussed. A study of known syntheses is very useful and provides a basis for the thoughts and strategies of the investigator (refer to Linderg's work, *vide supra*). As a teaching tool for the beginner, however, many points are glossed over or are not obvious. The next two sections will discuss first-time proposals submitted by students in a reactions/synthesis course that targeted securamine C (sec. 14.2) and variecolol (sec. 14.3).



The intent of this chapter is <u>not</u> to simply criticize the proposal, but rather to show common mistakes that creep into that first proposal. In each section there will be three parts. The first part is the proposal by the student, <u>as submitted</u>. The second part is a list of all reaction types proposed by the student, and the third is the instructor's critique. The comments in the critique are often aimed at specific chemical problems related to that target and will serve as only a brief review of some chemistry. Others, however, are more general and will hopefully illustrate things to avoid while planning a synthesis. The proposals are reproduced exactly as submitted to show the importance that a presentation can make to the visual and conceptual interpretation of the proposal.

There are many ways for the reader to approach this chapter. The reader could construct a synthetic proposal of before reading further. The reader could act as the reviewer and construct their own critique. Of course, one could simply read my comments about each proposal. It is my belief that an active role in reviewing each proposal will be far superior to a passive role. Compare my criticisms with your own. Agree or disagree! That is a good first step to a good proposal.

14.2 TOTAL SYNTHESIS OF SECURAMINE C

14.2.A The Proposal

This synthesis is reasonable, but there are some problems with the presentation. In several places there is the potential for side reactions that have not been addressed. In one or two places, the proposed reaction maybe difficult. In general, however, the proposal has a good literature basis.

I. Introduction

II. Retrosynthetic Analysis

Securamine C from the marine bryozoan *Securiflustra Securifrons* family has recently been isolated and characterized by researchers at the University of Copenhagen¹. This interesting hexacyclic structure is an indole-imidazole alkaloid from a family of alkaloids that has yielded important biological activity². This proposal outllines a total synthesis of **1**.



Scheme I Retrosynthetic Analysis

Our approach to the synthesis of **1** is shown in Scheme **1**. The crucial N_1 - C_{12} bond making reaction is based on a serendipitous discovery of a Japanese group working on the related Picraline alkaloid system³. Using an intermediate closely related to **32**, they were hoping to form a bond between C_8 (bearing the leaving group) and C_{20} (the 3-position of the indole); instead the bond was formed between the indole nitrogen and C_8 . The formation of this new six-membered ring resulted in an isopleiocarpamine-type skeleton similar to **31**. From there, under acetic acid/ammonium acetate conditions, C_{20} was protonated then N_1 attacked the resulting iminium function at C_{12} (the 2-position of the indole) to give the unusual skeletal structure analogous to **1**.

(1) **32** in turn can be made by opening of the yohimbane-type ring structure pictured in **33** with the use of cyanogen bromide.³ The C–D rings of yohimbane-type alkaloids are usually constructed by way of a Bischler-Napieralski reaction of an amide intermediate such as **34**.⁴ Not shown but critically important in the transformation from **34** to **33** is the construction of the 8-membered ring. It is envisioned that this difficult task can be accomplished using a radical McMurry coupling⁵. **34** can be made by subsequent alkylation and acylation of N1 on a tryptamine-type of precursor.

The synthesis begins with the known 6-bromoindole $2,^6$ which has recently been made in high yield from the 6-aminoindole using a Sandmeyer reaction (Scheme 2). After protection of the indole nitrogen as the Boc derivative,⁷ the electron rich three position of the indole moity can be alkylated with an alkyl halide using iron sulfate with hydrogen peroxide in DMSO to give $3.^8$ The nitrile can then be hydrolyzed enzymatically to the acetamide using the nitrile hydratase taken from the *Rhodococcus rhodochrous J1* organism.⁹ Intermediate **4b** can then be alkylated with the commercially available propionaldehyde **4b** in EtOH with sodium carbonate as base¹⁰ to give **5**. ② This alkylation attaches C_2-C_4 .



Construction of the C₂₁-C₄ Side Chain

From our retrosynthetic scheme we now need to attach C_8-C_{11} to N_1 in order to set up the construction of the medium sized ring *via* McMurry coupling. This C_8-C_{11} fragment

(intermediate **6**, **Scheme 3**) can be attached using a dicyclohexylcarbodiirnide (DCC) coupling of the carboxylic acid of **6** to N₁ in the presence of hydroxy-benzotriazole in DMF as the solvent.^{10,11} The synthesis of fragment **6** begins with known **6a**.¹² This interesting compound can undergo ozonolysis ③ with a reductive workup to give aldehyde **6b**,^{13,14} which can be hydrolyzed with potassium t-butoxide and water to give the carboxylic acid **6c**.¹⁵ Resolution of racemic **6c** will follow the protocol of Daniel Comins; the procedure calls for esterification with a chiral alcohol ⑤ to produce a pair of diastereomers which can be separated with a chiral HPLC column.¹⁶ The particular chiral alcohol to be used here is (+)-trans-2-(alphacumyl)cyclohexanol((+)-TCC). ④ The desired diastereomer will then be hydrolyzed to the carboxylic acid **6** using the *t*-butoxide/water conditions mentioned above. This hydrolysis would also regenerate the expensive chiral alcohol.



Dialdehyde was prepared with a view towards making the 8-membered ring which includes N_1 to C_4 and C_8 to C_{11} . These medium sized rings are notoriously difficult to make because of the transannular strain generated. The one called for here would be particularly difficult since the dimethyl group at C_9 would add an even greater dimension of steric hindrance. The method of choice to accomplish this task would be the use of a radical coupling, which has been successfully employed in the formation of a key 8-membered ring in the important taxol structure.¹⁷ Radical cyclizations are less susceptible to the steric effects which cause other methods to fail.⁵ For the present synthesis, 7 can be cyclized using a titanium induced reductive coupling of the two carbonyl units in the presence of a zinc-copper couple ⁽⁶⁾ using dimethoxyethane as solvent. The zinc-copper mixture is generated by adding zinc dust to a solution of copper sulfate in deoxygenated water.⁵

Once the C_4, C_8 diol is in hand, ⑦ the two hydroxy bearing carbons need to be differentially oxidized. The same C_9 methyl groups that would make the ring closure difficult could become an

asset in differentiating C_8 from C_4 . In particular, it may well be possible to oxidize the C_4 hydroxy group to the ketone and give **13** directly from **8**, without the need for the protection/deprotection method shown in **Scheme 4**. The Swern oxidation,¹⁸ for example, uses the bulky base TEA; this could lead to selective oxidation of C_4 , since C_8 should be sterically less accessible. Failing that, the method shown in **Scheme 4** could be employed. C_4 would be protected with a silyl group.¹⁹ Then the C_8 hydroxyl could be acetylated with acetic anhydride and pyridine.²⁰ Deprotection at C_4 with fluoride, followed by oxidation¹⁸ to the ketone with Swern conditions(oxalyl chloride and DMSO in methyene chloride followed by the addition of TEA), and finally deprotection of the acetate with potassium carbonate in methanol would give intermediate **13**.



The final target securamine contains a dou le bond between C_2 and C_3 . We would like to introduce that double bond after th important Sakai-type addition of N_1 to C_{12} since an sp² center at C_1 may adversely affedt that ring closure. The strategy employed here is to introduce a functional group at C_3 which can be easily transformed into the C_2 – C_3 double bond at a later stage. For this reason, **13** ③ will be converted to the selenide *via* addition of phenyl selenium chloride to the enolate generated at C_3 with LDA,²¹ to give **14**. ④ The selenide will be oxidized later and will eliminate thermally at mild temperature to give the olefin.

The hydroxy group at C_8 needs to be converted to a leaving group for eventual bond formation with the indole nitrogen. This can be done by conversion to the bromide **15** ① with thionyl bromide and pyridine in methylene chloride at ambient temperature²². The leaving group could just as easily have been tosylate by converting the hydroxyl group with tosyl chloride and base in methylene chloride.

The closure of the new 6-membered lactam ring to give **16** from **15** is based on extensive literature precedent from synthetic work in the yohimbane-type indole alkaloids.²³ The mechanism of this Bischler-Napieralski reaction involves conversion of the amide function to an imidoyl chloride, (12) (13) which makes C_{11} electrophilic enough to add to the two position of the indole.²⁴



In preparation for the important N_{13} (indole N)–C₈ bond forming reaction(**17** to **18**), the newly formed 6-membered ring of **16** must now be reopened with cyanogen bromide to give, after deprotection of the Boc group, intermediate **17**. (4) The stereochemistry at C₁₁ is critical because if the OR(in this case OBn) group is *alpha*(behind the plane of the page) then you will not get Sakai-type addition of N₁ to C₁₂ but rather N₁ will simply add back into C₁₁ to form the 6-membered ring again. With the OBn group at C₁₁ *beta*, as would be expected from the literature precedent, intermediate **17** is now poised for the immediate N₃–C₈ bond formation and subsequent Sakai ring closure.³ In the original paper the cyanogen bromide reaction was done in MeOH which gave an OMe group at C₁₁. In the current target, C₁₁ needs to ultimately become a methylene group. Towards that end, the cyanogen bromide reaction would be done in benzyl alcohol to give the benzyl ether at C₁₁, which can be removed(hydrogenolysis) and reduced(triethyl silane reduction of the ketone) more easily than the methyl ether.

(5) When 17 is subjected to sodium hydride in DSMO to generate the indole anion, the isopleiocarpamine-type skeleton 18 should be formed by the formation of the new sixmembered ring.³ In our case there is the danger that N_{13} could displace the C10 chlorine to give a new four-membered ring; modeling studies would need to be done to evaluate that possibility.



The target molecule contains an imidazolinone off of the C₄, C₈ positions. This heterocycle can be formed by adding a molecule of urea to an alpha-bromoketone. (5) (7) (18) Accordingly, intermediate **18** would be brominated with a radical process using Nbromosuccinimide in methylene chloride,²⁵ then urea (19) would be added under acetic acid conditions to give the new heterocycle.²⁶ Ammonium acetate in acetic acid would then complete the hexacyclic intermediate **21**.³ (29)



What is left to complete the synthesis of Securamine C is essentially the 2 reduction of C₁₁ to a methylene. Removal of the benzyl ether can be done by hydrogenolysis using palladium on carbon in ethanol.²⁷ Literature precedent shows that the oxidation of the resulting alcohol to the ketone using the Collins reagent(pyridine-chromium trioxide in methylene chloride) 2

would also oxidize the C_3 selenide to the selenoxide which would immediately eliminate under the reaction conditions.²⁸ Reduction of the C_{11} ketone with triethyl silane would complete the synthesis of **1**.

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14.2.B The Critique

The reaction types used in this proposal are as follows.

- 1. Bischler-Napieralski reaction (sec. 12.5.B).
- 2. McMurry coupling (sec. 13.8.F).
- 3. Sandmeyer reaction (sec. 2.11).
- 4. DCC coupling (not discussed in this book).
- 5. Ozonolysis (sec. 3.7.B).
- 6. Radical cyclization (sec. 13.7).
- 7. Birch reduction (sec. 4.9.E).
- 8. Swern oxidation (sec. 3.2.C.i).
- 9. Sakai coupling (not discussed in this book).
- 10. Selenoxide elimination (sec. 2.9.C.vi).
- 11. Alcohol to bromide with thionyl bromide (sec. 2.8.A).
- 12. N-Boc protection (sec. 7.3.C.iii).
- 13. NBS allylic bromination (sec. 2.8.B).
- 14. Alcohol protection benzyl ether (sec. 7.3.A.i).
- 15. Silane reduction of ketones (sec. 4.10.C).

The number of each critique appears in the body of the proposal as a circled number. The critique of this proposal is:

- 1. Do not begin a sentence with a number.
- 2. For the conversion of 4 to 5, the CHO group may not be compatible with this reaction? Does it have to be protected?
- 3. In the conversion of **6a** to **6b**, there may be a problem because zinc and acetic acid can reduce halides. There is a question as to whether or not the Cl will be reduced.
- 4. How will TCC be used? It would be appropriate to give some reaction conditions.
- 5. In the conversion of 5 to 7 there maybe a problem putting the second C=O on the amide. This can be difficult. The chloro-acid is rather hindered and there is a question whether this will have an effect on the reaction with DCC.
- 6. In the conversion to 8 the Cl adjacent to the carbonyl may be reduced?
- 7. What is the stereochemistry of the diol?
- 8. Since one secondary alcohol is adjacent to a gem-dimethyl unit, it might be possible to selectively oxidize the less hindered OH to the acyloin (compound **13**) without all those steps?

- 9. In the conversion of 13 to 14, the OH group probably requires protection.
- 10. Once the enolate is formed, is displacement of the chlorine across the ring possible?
- 11. In the conversion of 14 to 15, does thionyl bromide react with seleno ethers?
- 12. In the conversion of 15 to 16, this is actually 2 steps over the arrow, not one as shown
- 13. Will the chlorine survive this step?
- 14. In the conversion of **16** to **17** is seems unlikely that the SePh unit, the Cl unit, the Br unit will survive without some secondary reactions, particularly when TFA is being used.
- 15. In the conversion of **17** to **18 17** NaH may form the enolate at the O=C–C–SePh carbon. Although it may be less favored, it formation of a three-membered ring possible (see Favorskii rearrangement)? Can the enolate anion displace the Cl across the ring?
- 16. In the conversion of **18** to **19** bromine radicals are generated. Will the presence of the chlorine pose a problem?
- 17. Under these conditions, SePh can be lost to form a radical. Will this cause any problems?
- 18. It is also possible to brominate at the C bearing the SePh unit. To form the targeted bond requires displacement of bromide from a neopentyl carbon, which is very difficult
- 19. In the conversion of **19** to **20**, the new bond generating the heterocycle occurs at a qua ternary carbon. Can this occur as planned?
- 20. The Collins oxidation is applied to a hindered substrate. Will this cause problems?
- 21. In the conversion of 23 to 1 will Cl survive treatment with silane and TFA?
- 22. In the references, do not use et al cite all authors for each paper.
- 23. For the transformation of **18** to **1**, there is minimal discussion. This section should be expanded.
- 24. Note the typographical error.

14.3 TOTAL SYNTHESIS OF VARIECOLOL

This proposal is reasonable considering it is a difficult target. The main problems have to do with stereo-chemistry of proposed products and, in some cases, choice of reagents. There is at least one reaction, the last one, that is questionable, but in general it is a reasonable approach.

14.3.A The Proposal

I. Introduction

Variecolol (1), a new sesterterpene was recently isolated from the mycellium of *Emericella purpurea*.¹ Presently, a study of variecolol's ability as an agent for preventing and treating hypertension, cardiovascular and cerebrovascular diseases and renal disease is taking place.² However, variecolol can only be obtained by extraction from the mycellium of *Emericella purpurea*. This is due to the fact of variecoloactone's highly functionalized complex fused ring structure making its total synthesis rather difficult.



Herein is described a synthetic strategy to obtain the basic ring structure of variecolactone which can be applied to other natural products with a similar ring structure.¹

II. Retrosynthetic Analysis



The key features of the synthesis of variecolol are outlined retrosynthetically in Scheme 1. Working one step back from (1) gives the _-hydroxy-carboxylic acid (2). Manipulation of the double bond contained within the eight membered ring gives (3) followed by a ring closing

metathesis reaction utilizing Grubb's catalyst leads to (4). Cleavage of the indicated bond leads to Fragments A and B which can be synthesized using slightly modified literature procedures.



A. Synthesis of Fragment A

The complete synthesis of the known³ Fragment A will follow literature procedures and is outlined in Scheme 2. Bromoacetal (5) can be prepared following the procedure by Buchi and West.⁴ Condensation of acrolein with ethylene glycol in the presence of anhydrous hydrogen bromide affords the bromoacetal (5) in good yield. The bromoacetal (5) is then converted to the corresponding grignard⁵ (6) by treatment with magnesium in tetrahydrofuran at room temperature. Treatment of (6) with a mixture of the α , β -unsaturated ketone (7), cuprous

III. Synthesis of Variecolol

bromide and dimethyl sulfide in tetrahydrofuran yields the 1,4-addition product (8) after aqueous acidic workup in moderate yield. Treatment of (8) with the previously prepared⁶ lithium dialkyl cyano cuperate (9) adds stereoselectively in a Michael fashion to provide a mixture of (10) and (11) in a ratio of approximately 11:1 and in excellent yield, however, the major isomer is not the desired one. This problem can be circumvented using the methodology described by Piers⁷ and Oballa and the conformational studies of 4-hydrindanones done by Dana⁸ and co workers. The results of the work done by Dana and co workers suggest that (11) would be the thermodynamically more stable isomer and the rationale is logical: isomer (11) has the trans ring juncture and less gauche interactions when compared to (10) which has the cis juncture. Thus, isomer (11) can be obtained preferentially by treating the 11:1 mixture with sodium methoxide in methanol at 40 °C causing epimerization at the α -carbon and hence approximately yielding a 1:14 mixture of (10) and (11). Separation of the two epimers by flash chromatography gives pure (11) in modest yield. In summary, a literature precedent for the synthesis of Fragment A will be used and is quite convenient, setting the absolute configurations in three of the nine stereogenic centers in Variecolactone

B. Synthesis of Fragment B

The synthesis of fragment **B** will be done according to Scheme 3. The known hexacarbonyldicobalt complexed alkyne (12) will be prepared according to the work done by Krafft and co workers.⁹ First, 3-butyn-1-ol (13) will be converted to its *tert*-butyldimethylsilyl (TBS) ether by treating a mixture of (13) with TBS–Cl in triethylamine and DMAP. Treatment of the protected alkynol with *sec*-butyl lithium in THF followed by low temperature quench with ethyl chloroformate yields the alkynoate (14). The alkynoate is then complexed with dicobaltoctacarbonyl in petroleum ether to yield (12) in excellent yield.



Production of the tetrasubstituted cyclopentenone (**15a**, **15b**)) involves condensing the protected vinyl ether (**16**) with (**12**) via a Pauson-Khand reaction.^{10,11} (**1**) Studies on the Pauson-Khand reaction^{10,11} have shown that upon condensing an unsymmetrical alkene with an unsymmetrical alkyne in the presence of a cobalt carbonyl compound give rise to mixtures of diastereomers (Fig 1) with the bulkier substituents of the alkene and alkyne being α to the carbonyl of the cyclopentenone. However, the stereochemistry α to the carbonyl is unimportant as it will be lost in later steps. (**4**) The stereochemistry at the β position is important, and in both products gives the correct absolute configuration, thus, no separation is necessary.



The next step involves selectively deprotecting the trimethylsilyl ether to produce (17) by a method described by Bunce and Hertzler.¹² Their method involves treating TMS ethers with sulfonic acid type exchange resins which will remove the TMS group and not the TBS group.¹³

The two preceding steps serve to eliminate the hydroxyl group of (16) by first converting the alcohol to a bromine and then replacing the bromine with a hydrogen. The bromo analog will be made using a method described by Sacks and Aston¹⁴ for converting α -hydroxyketones to α -bromoketones. Thus, treatment of (17) with phosphorus tribromide yields the α -bromoketone

(18). Subsequent removal of the bromine and replacement with hydrogen to produce (19) will follow work done by Chikashita and Itoh.¹⁵ Their work involves using 1,3-dimethyl-2-phenylbenzimidazoline (DMBI) (2) as the reducing agent and is believed to go through a radical reaction mechanism. Through their studies, DMBI was shown not to react with other functioanlities contained within the α -bromoketones such as esters, α ,-systems, and ethers making this methodology attractive for this synthesis.



Removal of the TBS protecting group to produce (20), cyclization (21a, 21b), protection (22a, 22b), hydrogenation (23a, 23b), and rearrangement (24a, 24b) will follow the procedure done by Krafft and coworkers.⁹ The structure (25) they did this series of transformations on to produce (26) is very similar to (20) and we believe it to work without incident. ⁽²²⁾

Thus treating a pyridine/acetonitrile solution of (19) with hydrofluorous acid will lead O to (20) in excellent yield. Subsequent cyclization to (21a, 21b) (7) by treating (20) first with an ethanolic solution of sodium borohydride and cerium (III) heptahydrate, and second a two normal solution of hydrochloric acid. This reaction is predicted to be highly diasteroselective. Because of the methyl's orientation, hydride transfer will occur preferentially on the opposite face of the methyl. Protecting the alcohol again with the TBS group using TBS-triflate in pyridine produces (22a, 22b). Hydrogenation of this mixture is also predicted to be highly diastereoselective. With the bulky TBS group present, hydrogen should add across the double bond on the opposite face thus producing a mixture of (23a, 23b). (5) (8) The three step rearrangement process to form (24a, 24b) is as follows. Upon reducing the lactone moiety in the mixture from the previous step with diisobutyl aluminum hydride in toluene, gives a lactol which is then treated with ten equivalents of methyltriphenylphosphonium bromide and *n*-butyl lithium in THF to give the corresponding alkene. The large excess of vlide is required to avoid epimerization of the stereocenter adjacent to the aldehyde prior to the Wittig olefination. Oxidation of the primary alcohol using Jone's Reagent⁹ to the carboxylic acid, followed by refluxing in two normal hydrochloric acid will yield, by and Sn2 reaction, (24a, 24b). (9) Separation of the mixture of diastereomers by flash chromatography is predicted to yield pure (24a) in moderate yield. Ozonolysis of (24a) to produce (25) will follow the pioneering work done by Pappas and co workers.¹⁶ A mixture of (24a) in methanol is treated with ozonized oxygen followed by reductive workup with dimethyl sulfide to produce (25). The attractive methodology developed by Pappas and co workers has shown that carbonyl moieties present in olefinic compounds do not interfere with the oxidation by ozone. Reduction of the aldehyde moiety of (25) with sodium borohydride¹⁷ to produce the corresponding alcohol is a well known reaction in which the lactone group is known to be left unmolested by the reducing agent, will complete the synthesis of Fragment **B**.



C. D. Modification of Fragment A Before Condensation with Modified

Fragment B

The modifications of Fragment A which are required before it's condensation with Fragment **B** are outlined in Scheme 4. Conversion of Fragment A to (26) will follow a procedure described by Bailey and Khanolkhar.¹⁸ Their work (10) describes a procedure using potassium hexamethyldisilizane as a non-nucleophilic base to produce an enolate and subsequently substituting a methyl group α to the carbonyl of a phenyl ketone. Although the hydrogens at each α position of Fragment A are available for abstraction, it is predicted that the kinetic hydrogen will be removed due to the steric bulk of the base employed. Thus, treatment of Fragment A with KHMDS followed by methyl iodide will yield (26). Reduction of (26) with sodium borohydride¹⁷ in THF leads to the corresponding alcohol mixture (27). (1) Protection of this alcohol mixture with TMS-Cl¹⁹ to (28) prepares the fragment for subsequent ozonolysis¹⁶ to produce the ketone (29). Protection of this ketone with ethylene glycol²⁰ to make (30) followed

by deprotection^{9,17} (**31**) (1) and reoxidation^{9,17} (3) (32) prepares Fragment A to be condensed with the modified Fragment B. The above list of modifications indirectly protects the double bond of the isopropenyl group of Fragment A in order to conduct a ring closing metathesis utilizing Grubb's catalyst in later steps. Modification of Fragment B before Condensation with Modified Fragment A



The modifications of Fragment **B** which are required before it's condensation with Fragment **A** are outlined in Scheme 5. Fragment **B** will be converted to its TMS protected form (**33**) by the method cited above.¹⁹ Allylation of (**33**) to (**34**) ⁽⁴⁾ will follow a procedure described by Walton and Reid²¹ in their work of allylating γ -butyrolactone. Thus, treating (**33**) with LDA in hexane followed by HMPA and allyl bromide will produce (**34**). Deprotection⁹ of (**34**) to recover the alcohol moiety (**35**) followed by displacement with phosphorus tribromide¹⁷ to produce (**36**) prepares Fragment **B** to be condensed with the modified Fragment **A**.



E. Completion of the Synthesis of Variecolactone

The completion of the synthesis of variecolactone is outlined in Scheme 6. First, treatment of (32) with KHMDS¹⁸ is predicted to remove the -hydrogen adjacent to the methyl group due to the fact of the nature of the bulky base employed and the steric hinderance of the 1,3-dioxalane group adjacent to the other α -hydrogen. Once the enolate has formed it is predicted that the incoming electrophile will preferentially come in on the same face as the angular methyl (1) thus producing (37). If this prediction turns out to be wrong, the problem can be alleviated by first condensing Fragment A with (36) followed by methylation. Subsequent Wittig olefination²² \bigcirc of (37) to produce (38) under basic conditions will not molest the ketal or ester moiety. Cyclization of (38) using Grubb's catalyst will follow a procedure done by Prasad and Hoppe.²³ In their work, several 8-membered rings were synthesized containing ester and cyclic ether linkages using Grubb's catalyst. It is believed that their methodology can be applied in converting (38) to (39). The stereochemical outcome (6) concerning the hydrogen α to the ester is unimportant as it will be transformed to a double bond in a later step. Hydrogenation of (39) to (40) using Wilkison's catalyst²⁴ is predicted to occur on the same face as the angular methyl due to the bulky 1,3-dioxalane group present α to the prochiral center. Hydrogenation with Wilkinson's catalyst has also been show not to interfere with ester functionalities.



Incorporation of the double bond to produce (41) will follow work done by Bella and Pirgo²⁵ as well as Fallis and co workers.²⁶ Their work involves incorporating a double bond into saturated y-lactones containing a ketal group using phenyl selenium bromide followed by hydrogen peroxide and sodium hydroxide to execute a syn elimination to produce the double bond in conjugation with ester carbonyl. It is predicted that when (41) is enolized with LDA, the phenyl selenium bromide will preferentially approach from the bottom face due to the three angular hydrogens present α and β to the enolized carbon. Once treated with peroxide a and sodium hydroxide, the only hydrogen which can be abstracted is from the bottom face thus producing (41). Treatment of (41) with aqueous $acid^{17}$ will serve two purposes, to hydrolyze the ester $\textcircled{1}{3}$ and ketal moiety to produce(42). The next step will follow work done by Dutler and co workers in their work involving steroids. One key step of their synthesis was converting a α -hydroxy carboxylic acid to a α -hydroxy lactone by using a dilute solution of potassium hydroxide in methanol. It was also noted that the stereochemistry of the hydroxyl group was observed to invert upon completion of this transformation as well as the ketone moiety being left unmolested. It is predicted that this methodology will work on our system to produce (43) (9) with one possible problem and that is the stereochemistry of the hydroxyl group. If it turns out to be the wrong stereochemistry, Mitsunobu²⁸ conditions can be utilized to invert the hydroxyl group before the cyclization. Another Wittig olefination²² reaction on (43) shall complete the synthesis of Variecolactone.

Summary

In conclusion, a methodology has been presented to synthesize Variecolactone. More generally, a synthesis has been proposed to attain the complex fused ring structure of variecolactone which could be applied to other products with this similar structure.

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14.3.B The Critique

The reactions used in this proposal are as follows:

- 1. Grignard reactions (sec. 8.4).
- 2. Magnesium cuprate conjugate additions (sec. 8.4.D).
- 3. Higher order cuprates, conjugate additions (sec. 8.7.B).
- 4. Pauson-Khand reaction (sec. 13.11).
- 5. Alcohol protection trimethylsilyl ether (ec. 7.3.A.i).
- 6. DMBI reduction (not covered in this book).
- 7. Luche reduction (sec. 4.4.B).
- 8. Dibal reduction of lactones (sec. 4.6.C).
- 9. Wittig olefination (sec. 8.8.A).
- 10. Ozonolysis (sec. 3.7.B).
- 11. Sodium borohydride reduction of aldehydes (sec. 4.4.A).

- 12. Enolate alkylation of ketones (sec. 9.3).
- 13. Ketone protection dioxolane (sec. 7.3.B.i).
- 14. Jones oxidation (sec. 3.2.A.iii).
- 15. Enolate alkylation of lactones (sec. 9.3).
- 16. Conversion of alcohol to bromide with PBr₃ (sec. 2.8.A).
- 17. Olefin metathesis (sec. 13.9.E).
- 18. Selenoxide elimination (sec. 2.9.C.vi).

The Critique. The number for each critique appears in the body of the proposal.

- 1. There is a discussion about the stereochemistry of the Pauson–Khand, saying it give the correct stereochemistry. Is this speculation, or based on the two references in a similar or identical system? This needs to be specific.
- 2. Is DMBI compatible with conjugated ketones also?
- 3. Note typographical error.
- 4. For the cyclization step-it is not clear why the reaction is diastereoselective n this system, or what the selectivity will be. Use models to explain.
- 5. Why is this hydrogenation diastereoselective? Is it subject to equilibration or isomerization?
- 6. In the conversion of **19** to **20**, will the use of HF cause problems with the ester?
- 7. In the cyclization, use models and discussion to show that **21a** is the major product.
- 8. Prove the stereochemistry of **23a** and discuss the selectivity.
- 9. Is there a step missing in the conversion of 23 to 24?
- 10. While it is OK to cite a recent reference, this transformation was reported much earlier and the original reference should be cited –see House's book, for example.
- 11. Although the stereochemistry of **27** is not important for the final product, it is important for isolation and handling and there should be a comment.
- 12. Is the dioxolane unit stable to treatment with HF?
- 13. The conditions used with Jone's reagent include strong acid, which might cause problems if the contact time is long. There are many other oxidizing agents where this is not potentially a problem. Is one of them better?
- 14. What is the stereochemistry of the allylic unit in **34**?
- 15. The statement concerning stereochemistry of **37** requires proof use models?
- 16. Prove the stereochemistry of **39** to **40** using models?
- 17. Compound 37 contains a sterically hindered carbonyl. The Wittig reaction can be slow

in such systems and/or give poor yields. Is this a problem here?

- 18. This compound is a lactone, not an ester. When the lactone is treated with aqueous acid, it can open. However, the equilibrium of most five-membered ring lactones lies towards the lactone. Why should this behave differently, and can the equilibrium be manipulated to obtain the target?
- 19. It is not at all obvious that the transformation of 42 to 43 will work. It may have precedent, but there should be more discussion of this reaction, particularly regarding the stereochemistry of the system and the relative distance of the two reactive centers.
- 20. Why are the letters included with the references?
- 21. Reference 9. Krafft is misspelled.
- 22. This scheme indicates the sequence will follow the work of Krafft and that it is similar. More detail should be provided as to the similarities and particularly differences between the proposed work and the literature work. Specifically, the differences must be highlighted since they are a potential source of problems.
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