Dennis P. Curran, Ned A. Porter, Bernd Giese

Stereochemistry of Radical Reactions

Concepts , Guidelines, and Synthetic Applications

With a Foreword by
Ernest L. Eliel

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Foreword

Stereochemistry, which originated in the latter part of the 19th century, has had a remarkable renaissance in the last 40 years. This is probably due to the increased importance of organic synthesis, which, in turn, relates to the rise in importance of the pharmaceutical industry.

Because of the presence of often numerous chiral centers in natural products, diastereoselectivity is crucial in their synthesis. More recently, the realization that mirror image chemical compounds often differ substantially in their pharmacological properties has stimulated the development of methods of enantioselective synthesis.

When one surveys the literature of stereochemistry through the major pertinent textbooks of the postwar period, one realizes that the focus was initially almost exclusively on ionic processes: electrophilic and nucleophilic substitution and addition reactions and their reversal. Somewhat later pericyclic reactions came into purview. However, reactions involving radical intermediates are notoriously absent from these compendia. Until some 15 years ago the common wisdom among organic chemists was that radicals lack regio- and even chemoselectivity, not to mention stereoselectivity, and that their main and arguably exclusive usefulness was in a few chain reactions including radical initiated polymerizations.

All this has changed since about 1980. It was found that radical cyclization and addition reactions can often be carried out cleanly, notably in the presence of very efficient chain transfer reagents, such as tributyltin hydride, that prevent the formation of oligomers and polymers in radical additions to olefins. Subsequently it was found that, given the appropriate environment, such reactions can proceed with high stereoselectivity. The same tenets of conformational analysis that have proved useful in constructing schemes for stereoselective ionic reactions apply to radical processes as well. This, under appropriate circumstances, includes the use of chiral auxiliaries to effect enantioselective syntheses.

The three authors of the present book have played important roles in the development of stereoselective radical reactions. All three, individually, have previously written reviews on the subject. It is fortunate for organic chemists that they have now teamed up to write the first comprehensive book on the stereochemistry of radical reactions and its applications.

Ernest L. Eliel
June 1995

Preface

The study of stereoselective radical reactions has been a microcosm of the larger field of application of radical reactions in organic synthesis—a period of neglect has been followed by swift progress and exciting developments. The purpose of this book is to review the status of the field of stereoselective radical reactions. While diastereoselective radical cyclizations and reactions of cyclic radicals have been common for some time, it had been thought until recently that levels of stereoselectivity in these reactions would be low, allowing of course for a few exceptions. Acyclic diastereocontrol has emerged only recently, but progress has been rapid. Enantioselective reactions of radicals are rare at present, but we believe that their development is now inevitable. We submit that stereoselective radical reactions are no different from other types of reactions—that they come in many flavors and at all levels of selectivity. The goals then become to learn which reactions will occur with high selectivity, and why.

In line with the title of the book, we will attempt to present the concepts that are needed to understand stereoselective radical reactions and the guidelines that are helpful to apply them. We will suggest repeatedly that stereoselective radical reactions can be understood, even predicted, by combining standard principles of conformational analysis of organic molecules with knowledge of structure and reactivity of radicals. We will illustrate these concepts and guidelines with synthetic applications that show how stereoselective radical reactions can be used to solve synthetic problems. We hope that the book will expand awareness of existing classes of stereoselective radical reactions and stimulate the development of new ones.

It is the thesis of this book that stereoselective radical reactions are both interesting and significant in their own right. The study of such reactions leads to a better understanding of the structure and reactions of organic radicals and opens new methods for the stereoselective synthesis of organic molecules. Furthermore, because there exist qualitative analogies between radical reactions and related ionic and pericyclic reactions, and because stereoselective radical reactions are often easier to understand and explain than their ionic and pericyclic counterparts, the stereoselectivity of radical reactions is of special interest across the field of asymmetric synthesis.

Therefore, the significance of stereoselective radical reactions spans the fields of stereochemistry and asymmetric synthesis.

We would like to gratefully acknowledge all the help that we received in preparing the text and figures for this book from Michele Russo, Suzanne Curran, Anne Ghosez-Giese, and Kitty Porter. We also thank our graduate students and postdoctoral coworkers, who helped in the proofreading of the book. Dennis Curran would like to thank the University of Basel for a "Reichstein Visiting Professorship" that greatly facilitated his contribution to the book. Ned Porter acknowledges receipt of an Alexander von Humboldt Senior Fellowship and the kind hospitality of Professor Dr. Christoph Rüchardt while this book was being written.

Dennis P. Curran, Ned Porter, Bernd Giese
July, 1995

Abbreviations

Ac	acetyl
AIBN	azobisisobutyronitrile
Ad	adamantyl
Ar	aryl
Bn	benzyl
Bu	butyl
Bz	benzoyl
Cbz	carbobenzyloxy
DBU	diazabicycloundecane
DHP	dihydropyran
DME	dimethoxyethane
DTBP	di-*t*-butylperoxide
e^-	electron
Et	ethyl
Fmoc	fluorenylmethyloxy carbonate
HMPA	hexamethylphosphortriamide
Im	imidazolyl
LDA	lithium diisopropylamide
mCPBA	*m*-chloroperbenzoic acid
Me	methyl
NBS	N-bromosuccinimide
$OGlu(OAc)_4$	tetraacetylglucoside
PCC	pyridinium chlorochromate
Pr	propyl
PTOC	pyridine-2-thione carbonate
TBHP	*t*-butylhydroperoxide
Tf	trifluoromethanesulfonyl
Th	thiohydroxamate
THF	tetrahydrofuran
THP	tetrahydropyranyl
TMS	trimethylsilyl
Tol	*p*-tolyl
TTMS	tris(trimethylsilyl)silicon hydride

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Chapter 1

Radical Reactions in Organic Synthesis

1.1 Introduction

As recently as a decade ago, organic radicals were regarded as interesting reactive intermediates with limited synthetic potential. As a rule, radical reactions were thought to be "messy", and the few "clean" radical reactions, like allylic and benzylic brominations with *N*-bromosuccinimide (NBS), were viewed as the exceptions that proved the rule. This view of radicals probably arose because of the notion that highly reactive intermediates could not be selective. The concept of selectivity pervades organic synthesis, and with good reason—selectivity is the key to high yields.

The logic that reactive intermediates such as radicals cannot participate in selective reactions with controlled, predictable outcomes is faulty. Research on the structures and reactions of organic radicals conducted largely by physical organic chemists in the 60s and 70s[1] laid the foundation for the synthetic explosion that followed in the 80s and is still ongoing.[2] Synthetic chemists gradually came to realize that it is only relative rates that are important for selectivity; the simple fact that radicals often react with high absolute rates is actually desirable, not undesirable. They began to realize the difference between radical/radical reactions, which often occur at the diffusion-controlled limit and are hence unselective, and radical/molecule reactions, which occur with a huge range of rate constants. They learned that the rates of radical/radical reactions are easily minimized by choosing reaction conditions in which radical concentrations are low, and that the rates of radical/molecule reactions—that is, the selectivities—can be adjusted by the experimenter over a wide range by choice of reaction partners, concentrations, temperature, and other variables.

Radical-molecule reactions are now recognized to frequently be both chemo- and regioselective. It is ironic that radical reactions, once thought to be capricious and unpredictable, have a higher level of predictability in

complex settings than most other types of reactions. This predictability is due to the large body of knowledge of radical rate constants[3] and substituent effects in simple systems, and to the fact that these effects in simple systems can often be translated to complex systems in a straightforward fashion.

The idea that radical reactions cannot be highly stereoselective has been the last perceived selectivity barrier to fall. Indeed, this selectivity barrier is more than just perceived. Consider that a reaction providing a 95/5 ratio of diastereomers at room temperature requires an energy difference in the two diastereomeric transition states of 1.7 kcal/mol. If one views this energy difference as a percentage of the activation barrier, then transformations like Diels–Alder reactions, which typically have activation barriers of 25–35 kcal/mol, should be much easier to render stereoselective than radical reactions, which typically have activation barriers of 5–15 kcal/mol. On the other hand, consider that there are many very rapid organic reactions with low activation barriers (enolate alkylations, aldol reactions) that are routinely used in both diastereoselective and enantioselective synthesis. It has been our premise for some time that radicals are normal organic species subject to the same types of steric, electronic, and stereoelectronic interactions as all other organic molecules, and that these interactions can be both understood and used in a predictable fashion to control stereochemistry. This premise underlies the entire book.

The purpose of this book is to review the status of the field of stereoselective radical reactions. While diastereoselective radical cyclizations and reactions of cyclic radicals have been common for some time, it had been thought until recently that levels of stereoselectivity in these reactions would be low, allowing of course for a few exceptions. Acyclic diastereocontrol has emerged only recently, but progress has been rapid. Enantioselective reactions of radicals are rare at present, but we believe that their development is now inevitable. We submit that stereoselective radical reactions are no different from other types of reactions—that they come in many flavors and at all levels of selectivity. The goals then become to learn which reactions will occur with high selectivity, and why.

In line with the title of the book, we will attempt to present the concepts that are needed to understand stereoselective radical reactions and the guidelines that are helpful to apply them. We will suggest repeatedly that stereoselective radical reactions can be understood, even predicted, by combining standard principles of conformational analysis of organic

molecules[4] with knowledge of structure and reactivity of radicals. We will illustrate these concepts and guidelines with synthetic applications that show how stereoselective radical reactions can be used to solve synthetic problems. We hope that the book will expand awareness of existing classes of stereoselective radical reactions and stimulate the development of new ones.

1.2 Principles of Radical Reactions

To understand stereoselectivity in radical reactions, it is first necessary to have a general understanding of the principles of radical reactions and how these principles impact on synthetic planning. There are a number of excellent books and reviews that treat this topic in depth.[5–8] The goal of this section is to briefly recap some of the most important features of radical reactions in synthesis. Readers with significant experience in radical chemistry may wish to skip this section, while those with little experience may wish to augment it with additional information in the more comprehensive treatments.

1.2.1 General Considerations

Most of the radicals used in synthesis are transient, and they react with each other and with any other radicals present in the medium at the diffusion-controlled limit. For this reason, reaction conditions are usually chosen so that radical/radical reactions are avoided. Radical/molecule reactions are often conducted in chains, but methods based on oxidation and reduction are also important.

Radicals are now valued synthetic intermediates[9] because they can be used for transformations that are often difficult to accomplish by other means and because these transformations typically occur under very mild conditions where both selectivity and tolerance of functional groups are high. The kinds of protection schemes that are often essential for synthetic sequences of ionic reactions are rarely required for radical reactions; carbonyl substituents and heteroatom-hydrogen bonds (OH, NH) do not usually pose problems in radical reactions. However, protecting groups may still be required for other steps in a synthetic sequence, and nearly all popular classes of protecting groups are tolerated in radical reactions. The kinds of

β-elimination reactions and 1,2-shifts that pervade anionic (organometallic) and cationic chemistry are rare in radical chemistry, and their occurrence is readily predicted.

1.2.2 Medium and Temperature Effects

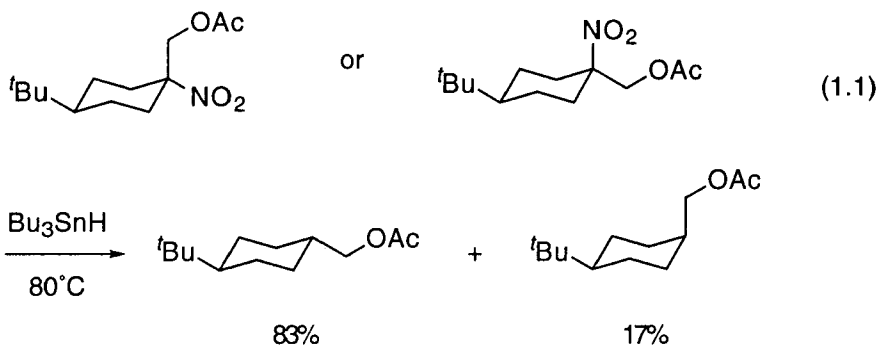
Since most radical reactions show small solvent effects, the choice of solvent is dictated not by the solvent effect on selectivity, but by other concerns. Though the rates of radical/molecule reactions are limited in principle by competing radical/radical reactions, the concentrations of radicals are so low that it is often the rates of radical/solvent reactions that limit the types of radical/molecule reactions that can be conducted. The choice of solvent is therefore dictated by the expected velocity of the desired reaction. With the exception of solvents like benzene (which reacts by radical addition), most solvents react with radicals by hydrogen atom transfer. For the slowest possible radical/molecule reactions, solvents like benzene, *tert*-butylbenzene, and *tert*-butyl alcohol are preferred. Because of its strong O–H bonds, water is also an excellent solvent for radical reactions if the reactants are soluble. This also means that dry solvents are not required. DMSO, acetonitrile, and methylene chloride are also useful. As the rates of the reactions to be conducted go up, the list of useful solvents expands to include almost all the popular organic solvents including alkanes, alcohols, ethers, and halocarbons. Supercritical CO_2 shows promise as an environmentally benign solvent for radical reactions.[10]

Temperature effects are of crucial concern for stereoselective reactions. Like many other transformations, radical reactions often provide increasing levels of stereoselectivity at lower temperatures, although the amount of improvement varies from reaction to reaction. Whether or not a given chain will propagate at low temperatures depends upon the rate of the slowest reaction in the chain. Cooling reduces the rates of all reactions, and chain propagation steps that were efficient at 80°C may no longer be fast enough at room temperature or –80°C. In short, the faster the steps that are involved in the chain, the lower the temperature at which the chain will still propagate. Chains will always get shorter at lower temperatures, so compensation by increased initiation is often required. There are now a number of chemical[11] and sonochemical[12] initiation methods that can be used to conduct chain reactions at low temperatures. Non-chain radical reactions can be conducted

at any temperature, provided of course that the rates of radical generation and reaction are rapid enough.

1.2.3 Stereochemical Features of Carbon-Centered Radicals

Stereochemical information associated with a bond to a radical precursor is usually lost upon formation of the radical. In other words, radical reactions are not stereospecific. Most alkyl radicals are thought to be either planar or very slightly pyramidal with a tiny barrier to inversion.[13] With a few exceptions (like cyclopropanes), stereoisomeric radical precursors generate the same radical and ultimately provide the same products. A typical example of the identical reactions of a cyclohexyl radical generated from both axial and equatorial precursors is shown in Equation 1.1.[14] Many other stereoisomeric cyclic and acyclic radical precursors behave likewise.



Electronegative substituents (oxygen, halogens, etc.) cause a radical to pyramidalize and raise its barrier to inversion. However, the inversion barrier generally remains low enough so that the same equilibrating mixture of pyramidal radicals is formed from either isomeric precursor. π-Conjugated alkyl radicals are generally held to be planar. Vinyl radicals are usually thought to be bent and rapidly inverting,[15] though inversion can become slow with electronegative substituents.[16] Certain π-conjugating substituents (like aryl groups) favor a linear structure for vinyl radicals.

The lack of stereospecificity in the reactions of stereoisomeric radical precursors can be viewed as a disadvantage (product configurations cannot be controlled by precursor configurations). But in another important sense it is a significant advantage: there is no need to develop a stereoselective

synthesis of the precursor. Reactions of either isomeric precursor or a mixture of both usually give the same results. (However, while the isomeric precursors generate the same radical, the rate of radical generation may not be the same.)

The two common scenarios for stereoselection in radical reactions are shown in Figure 1-1. The diagrams assume that there are two possible stereoisomeric products, P^1 and P^2, and that each is derived from a single transition state. The interconverting radicals (case 2) and the isomeric reaction products (cases 1 and 2) are arbitrarily shown as being equal in energy. For a planar alkyl (or linear vinyl) radical (case 1), a single intermediate can access two diastereomeric transition states. For a pyramidal alkyl (or bent vinyl) radical (case 2), each interconverting intermediate accesses a single isomeric transition state. Case 2 is a typical example of Curtin–Hammett kinetics.[17] The smaller the barrier to interconversions of the intermediates in case 2 and the closer these intermediates are in energy, the more similar the two scenarios become. However, transition states derived from pyramidalized radicals will probably have increased pyramidalization compared to those from planar radicals, and this can have stereochemical consequences for the relative energies of stereoisomeric transition states.

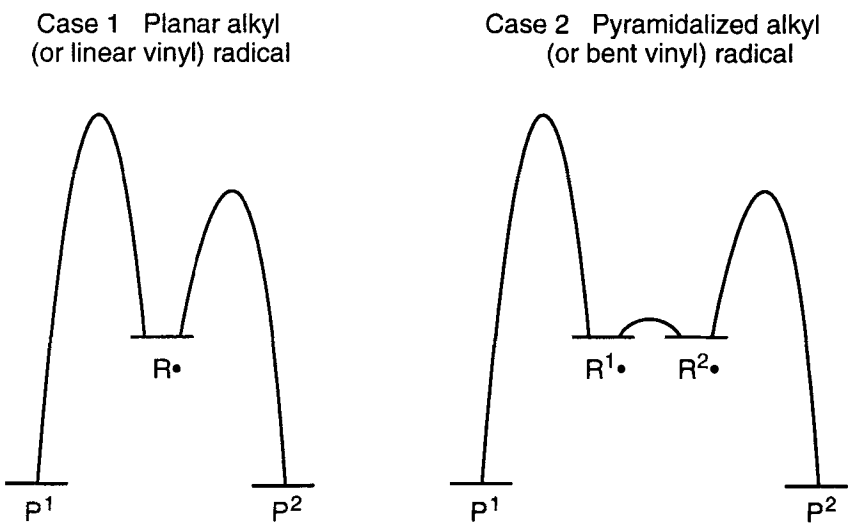


Figure 1-1. Energy Diagrams for Stereoselective Radical Reactions.

The case 2 scenario also applies to planar radicals that have different conformations as a result of a ring flip or bond rotation, but in reality this situation is often more complex. For example, in typical reactions of π-conjugated radicals with adjacent stereocenters (1,2-asymmetric induction), the radical has as many as three different conformations generated by rotation of the σ-bond adjacent to the radical. If each of these is allowed to be attacked from either face, then six different transition state conformations must be considered. However, it is usually possible to rule out higher energy conformations by using standard principles of conformational analysis, and thereby reduce the number of likely transition state candidates to two or three. The difficult part is evaluating the relative energies of these candidates.

The structure of a radical is then a key factor controlling the outcome of its reactions to provide stereoisomeric products. Information about radical structures typically comes from two sources: ab initio or semi-empirical calculations and ESR spectroscopy. Calculations on open shell structures, whether ground state or transition state, pose some additional problems compared to closed shell species, but they are being used more and more frequently and with evident success. ESR spectroscopy provides direct spectroscopic information about a radical under study or about a suitable model. Like NMR spectroscopy of closed shell molecules, ESR spectroscopy can provide useful information about both the structure and the conformation of a radical. Taken together, ESR spectroscopy and calculations make an especially powerful tool that will be used in subsequent chapters on a number of occasions to interpret results.

1.2.4 Reactions of Radicals

Aside from oxidations (to give cations) and reductions (to give anions or organometallic species), most radical/molecule reactions can be grouped into one of two large classes: 1) atom and group transfer reactions (sometimes called abstractions, homolytic substitutions or S_H2 reactions), and 2) additions to π-bonds (or the reverse, which is usually called a β-fragmentation or a β-elimination). The diversity that is available from the reactions of radicals comes from the broad range of reactants that participate in these two fundamental classes of reactions.

In the first class of reactions, an atom or group is transferred from a closed shell molecule to a radical to provide a new closed shell molecule and a new radical (Eq. 1.2). Univalent atoms, especially iodine, bromine, hydrogen, and to a lesser extent chlorine, are frequently transferred in homolytic substitution reactions, as are chalcogenide groups like TeR, SeR, and, to a lesser extent SR. These reactions are frequently assumed to be concerted, as shown in Equation 1.2, although there is little direct experimental evidence to support this assumption. The rates of these types of reactions typically parallel their exothermicity. With a few significant exceptions (such as iodine transfer), endothermic reactions do not occur, so most homolytic substitutions are irreversible under typical preparative reaction conditions. Within a series of reactions of comparable exothermicities, reactions of the pairs with weaker forming and breaking bonds typically occur faster than those with stronger forming and breaking bonds. For example, iodides are usually transferred much faster than bromides and phenyl selenides are transferred faster than phenyl sulfides. Favorable polar effects can accelerate atom or group transfer reactions just as unfavorable polar effects can decelerate them.

$$A\text{–}X + \bullet R \rightleftharpoons A\bullet + X\text{–}R \qquad (1.2)$$

X = I, Br, Cl, H, TeR, SeR, SR

Radical addition-elimination reactions come in many varieties (Eq. 1.3), and the rates of these processes are determined by an interplay between enthalpic, steric, and polar effects. Additions of carbon-centered radicals to alkenes and alkynes are usually exothermic and irreversible. These reactions are important in synthesis and they have been the subject of much study from the standpoint of substituent effects on rates.[18] The importance of polar effects (pairing of nucleophilic radicals with electron poor alkenes, or the reverse) and steric effects are now well recognized. Enthalpic effects had been considered to be of lesser importance for some time, but they are making a comeback of late.[19] Additions of carbon radicals to carbon heteroatom multiple bonds (CN, C=O, C=S) can be reversible. The addition of a radical to a π-bond followed by fragmentation of a different bond accomplishes a group transfer reaction, though by a different mechanism from the homolytic group transfer reactions described above.

$$A\bullet + C{=}X \rightleftharpoons A{-}C{-}X\bullet \qquad (1.3)$$

A = Carbon or heteroatom-centered radical
X = Carbon or heteroatom

Additions of heteroatom-centered radicals such as I•, Br•, PhS•, and R_3Sn• to carbon-carbon bonds are frequently reversible, in part because the addition reactions of these radicals form weaker bonds than additions of carbon-centered radicals.

For intramolecular radical additions (radical cyclizations), the enthalpic and entropic effects of ring size and geometry are superimposed on the enthalpic, polar, and steric effects. Some of the key trends for radical cyclizations will be summarized in Chapter 2 for different ring sizes.

Figure 1-2 summarizes some very basic transition state models for radical reactions on which more sophisticated models for stereoselection often build. Radical atom transfer reactions probably proceed through a transition state where the forming and breaking bonds are roughly linear.[20] The reactions are usually thought of as concerted, but the possibility exists that the indicated transition state is actually an intermediate in a shallow energy well, especially for atoms like bromine and iodine. Group transfer

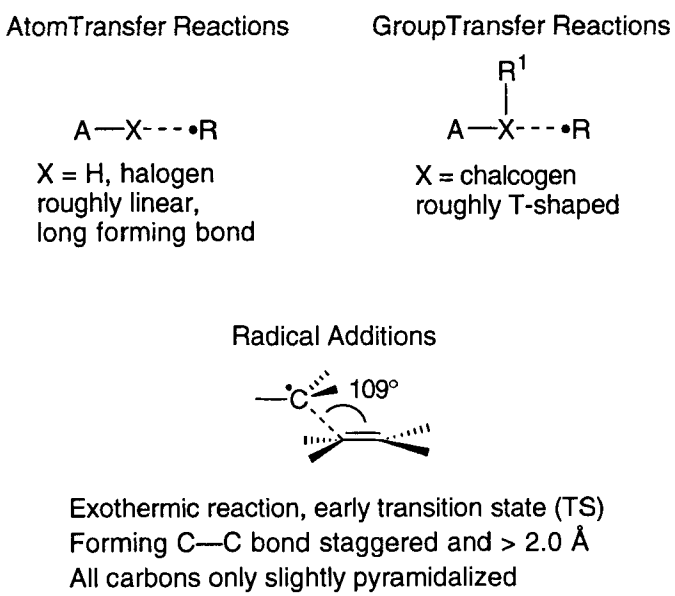


Figure 1-2. Basic Transition State Models for Radical Reactions.

reactions of chalcogenides are thought to proceed through T-shaped structures, although there is still discussion about whether these structures are transition states or intermediates.[21] Most synthetically useful reactions in this class are rapid and are expected to have early transition states with long forming bonds. The long forming bond and the linear transition state minimize the steric interactions between the incoming group and the radical leaving group, and even reagents like Bu_3SnH tend to behave as if they are small.

The transition structures for additions of carbon-centered radicals to alkenes have been determined at very high levels of theory. The picture that emerges is similar for the additions of nucleophilic and electrophilic radicals.[22] The approach vector of the radical to the alkene is close to 109°. And even though the forming C–C bond is very long (> 2.0 Å), the substituents about this bond are staggered. Because these transition states are early, the sp^2 atoms of the alkene are only slightly pyramidalized. The amount of pyramidalization of the radical presumably depends on the structure of the radical and on its ease of pyramidalization. Calculations suggest that simple alkyl radicals are only slightly pyramidalized at the transition state.[19,22]

1.3 Methods to Conduct Radical Reactions

While there are many different types of transformations that can be accomplished through the intermediacy of radicals, there are relatively few methods to conduct radical reactions. Suitable methods must: 1) generate radicals from non-radicals, 2) allow these radicals sufficient time to react, and 3) trap radicals to form stable closed shell products prior to the occurrence of radical/radical, radical/solvent, or undesirable radical/molecule reactions. The requirements sound stringent, but rate constants for many of the most popular types of reactions are now available, and it is usually not difficult to decide which method is appropriate and even to select suitable reaction conditions in advance.

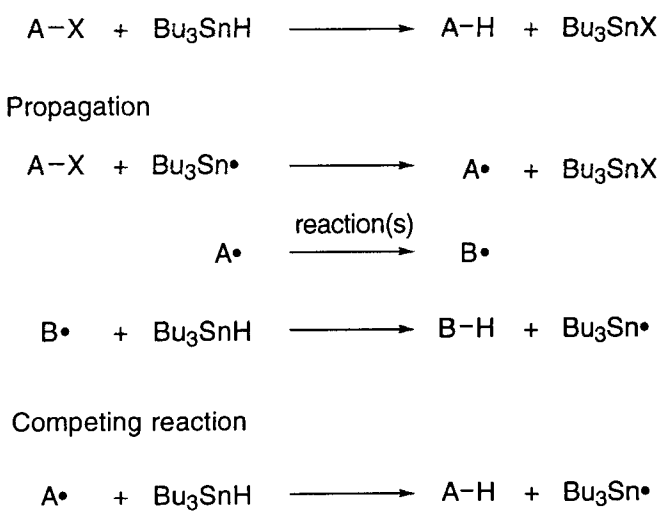
The following sections briefly review the methods that have been most commonly used to conduct stereoselective radical reactions. The presentation is designed more to refresh the memory of the reader, rather than to provide a detailed introduction. Such introductions are available elsewhere.[3,5–9]

1.3.1 Chain Methods

Radical reactions are most commonly conducted in chains because the chain transfer step conveniently links the generation of an initial radical from a radical precursor with the trapping of a final radical to make a stable product. Radical concentrations are limited by the rate of initiation, which is typically slow. Therefore, radical/radical reactions are uncommon.

1.3.1.1 Tributyltin and Tris(trimethylsilyl)silicon Hydride

These two compounds are the most popular among an increasing collection of reagents for conducting reactions by the "metal hydride" method. Equation 1.4 shows the chain for tributyltin hydride (Bu_3SnH),[23] and an analogous chain can be written for tris(trimethylsilyl)silicon hydride ($(TMS)_3SiH$ or TTMS).[24] Abstraction of a suitable radical precursor X by the tributyltin radical ($Bu_3Sn\bullet$) generates the initial radical A•, which then suffers a transformation (or series of transformations) to provide a new radical B•. Hydrogen transfer then forms the final product B–H and regenerates the tributyltin radical to continue the chain.



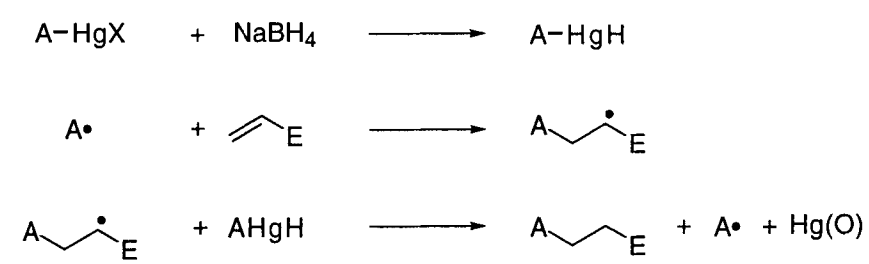
The standard problem in tin and silicon hydride reactions is the premature reduction of A• (or another intermediate radical) by the reagent. If the rate of conversion A• to B• is slow, then it is common to use low

concentrations of the hydride reagent to reduce the rate of the competing reduction. In this regard, the use of tris(trimethylsilyl)silicon hydride can be advantageous because it is a poorer hydrogen donor than tributyltin hydride so lower rates of hydrogen transfer are achieved at higher overall reaction concentrations.[24] Tin reagents are toxic and it can be difficult to completely free reaction products from tin, so tris(trimethylsilyl)silicon hydride can have practical advantages as well. From the standpoint of reactivity, the two reagents are similar but not identical. For example, TTMS hydrosilylates alkenes, alkynes, aldehydes and ketones much more readily than tributyltin hydride hydrostannylates them.

Related reactions of in situ generated mercuric hydrides have also frequently been used to probe issues of stereoselectivity. These reactions are easy to conduct at 0–25 °C, and are rapid, clean, and easy to work up and purify. This transformation is typically used for the addition of a nucleophilic radical to an electron poor alkene, as summarized in Equation 1.5.[25]

(1.5)

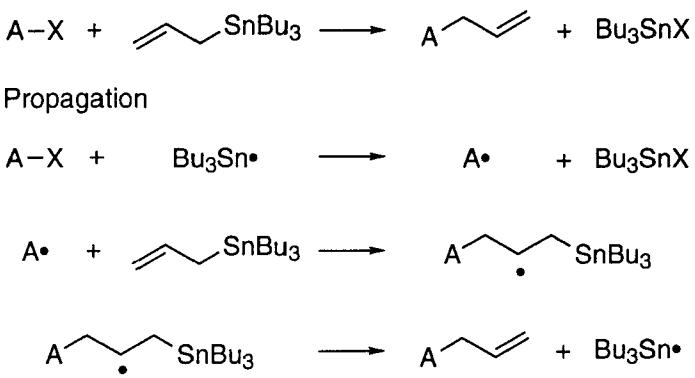
Mechanism



1.3.1.2 Allyltributylstannane

This reagent is the most popular among those in the class of reagents belonging to the "fragmentation method". The accepted chain mechanism for allylation with allyltributylstannane is shown in Equation 1.6. Abstraction of X by the tributyltin radical is followed by addition of radical A• to allyltributylstannane. Rapid β-fragmentation then provides the allylated product and the tributyltin radical. This method has many of the

advantages of the metal hydride method without the associated liability of premature trapping by the metal hydride. Since the addition of most radicals to allyltributylstannane is not an especially fast reaction,[26] it is often possible to conduct one or more reactions in between radical generation and allylation. The power of the allylstannane method lies in the fact that the chain transfer reaction (β-fragmentation) is rapid and unimolecular. This differentiates the final radical from all other radicals. Many of the most sophisticated sequences of radical reactions capitalize on this selectivity asset. Reactions with allyl stannanes are very easy to conduct,[27] and a number of related reagents are also used.[28] Vinylations can also be accomplished by the fragmentation method.[29]

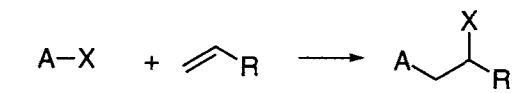


1.3.1.3 Atom and Group Transfer Reactions

Transformations in which the chain transfer step involves a homolytic substitution of a product radical with one of the precursors belong to the "atom (or group) transfer method". Aside from an initiator, these reagents do not require any other added reagents. While hydrogen atom transfer reactions are well known, they have limited synthetic usefulness. Most stereoselective reactions in this class involve transfer of a halogen atom (usually Br or I) or a phenylselenium group.

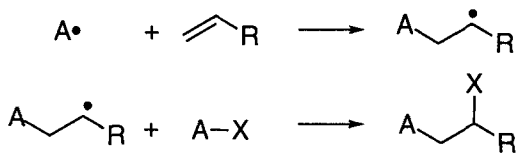
A generalized mechanism for this class of reactions is shown in Equation 1.7. The atom or group in A–X is both the radical precursor and the radical trap, and the molecular formula of the product is typically the sum of the molecular formulas of the starting materials. This method has the

advantage that there is no competing reaction for radical A• (so slow reactions are readily conducted) but the disadvantage that the key atom transfer step must be fast enough to propagate the chain (the more exothermic, the better). The body of knowledge on rate constants and substituent effects of atom transfer reactions is useful for planning rapid chain transfer steps.[30]



(1.7)

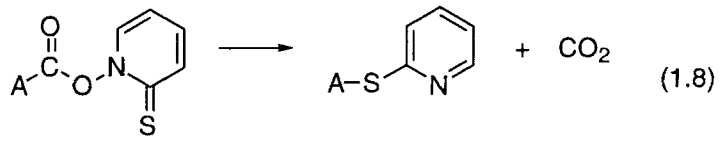
Propagation



1.3.1.4 Thiohydroxamates

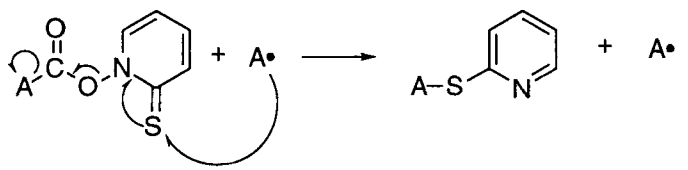
The "thiohydroxamate method" (sometimes called the "Barton method") involves a thiopyridyl group transfer reaction, but it differs from the reactions above in that the group is transferred by an addition/elimination mechanism rather than a homolytic substitution (Eq. 1.8).[31] Thiohydroxamate precursors are usually derived from carboxylic acids, and a decarboxylation occurs during the course of the reaction. In its simplest incarnation, the thiohydroxamate method is a decarboxylative thiopyridylation; the precursor thiohydroxamate ester serves as the trap for the product radical. Other reactions of radical A• (addition, cyclization) are possible provided that they are faster than reaction with the precursor. Furthermore, addition of better radical traps (X–Y) than the precursor provides an assortment of other products. In all of these more sophisticated reactions, the competing reaction of the initial radical A• with the thiohydroxamate can be minimized by keeping a low concentration of the thiohydroxamate.

Basic reaction

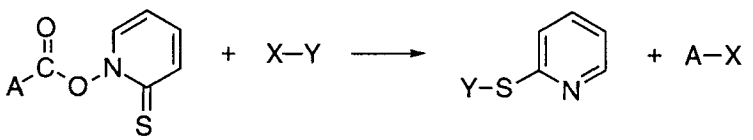


(1.8)

Propagation



Added traps



1.3.2 Non-Chain Methods

Non-chain methods can involve radical/radical coupling, oxidation, or reduction. There are many variants of these types of reactions, and collectively they have been used only occasionally in stereoselective synthesis. Key features of individual reactions will be presented in relevant sections as needed. General discussions of the features of these reactions and how these features differ from chain reactions are available.[6]

Radical/radical coupling can only be selective if the rates of all possible couplings are not the same. This situation is usually established by using a persistent radical whose concentration builds to a level where it can selectively trap transient radicals. Reactions of organocobalt complexes are good examples of this method.[32] Oxidative methods are often based on $Mn(OAc)_3$ and related reagents, and they generate radicals by oxidation of an enol or related intermediate and trap them by oxidation to a cation or by (oxidative) ligand transfer.[33] Reductive generation of radicals is usually followed by reductive trapping to form "anions" (organometallic reagents). Many one-electron reducing agents have been used; samarium(II) diiodide

and related reagents have a number of attractive features that have made them popular of late.[34]

1.4 Comparisons of Stereoselective Radical Reactions with Ionic and Pericyclic Analogs

This book will promote the view that the comparison of stereoselective radical reactions with related ionic and pericyclic reactions is informative and instructive. A nice example is provided by the rapid development of stereoselective radical reactions in acyclic systems, where the thoughtful borrowing of design features from known ionic and pericyclic reactions resulted in very rapid progress (Chapters 4 and 5). As the knowledge of stereoselective radical processes increases, it now becomes possible to reverse the direction of information flow: to use knowledge from radical reactions to interpret existing or to design new ionic and pericyclic processes.

Illustrative examples of the productive interplay in both directions come from analogies between α-carbonyl radicals and related acrylates and enolates. These analogies are drawn in several chapters of the book. Spectroscopic studies and crystal structures of chiral acrylates have provided information on the shape of these molecules that has led to suggestions of how stereochemistry is controlled in pericyclic reactions. Combining this information with the expected geometric similarities of acrylates and α-carbonyl radicals in turn suggested which kinds of chiral radicals would give good levels of asymmetric induction and why. For example, the model for the stereoselective cycloaddition reactions of acrylate derivatives with Oppolzer's camphor sultam suggested that this would be a good chiral auxiliary in radical reactions—a suggestion that was borne out by experiment (Eq. 1.9). A number of other chiral auxiliaries have been similarly either transferred into radical chemistry or designed from scratch (see Chapter 5).

There are also a number of analogies in 1,2-asymmetric induction between the reactions of α-carbonyl radicals and related enolates (Eq. 1.10, see Chapter 4). In analyzing these analogies, we view the radical as a model for an imaginary enolate whose reactions are free from solvent, counterion, and aggregate effects. Freed from these effects, the reactions of the radical are easier to understand. The existence of a sustained stereochemical parallel between the reactions of a chiral radical and a related chiral enolate suggests