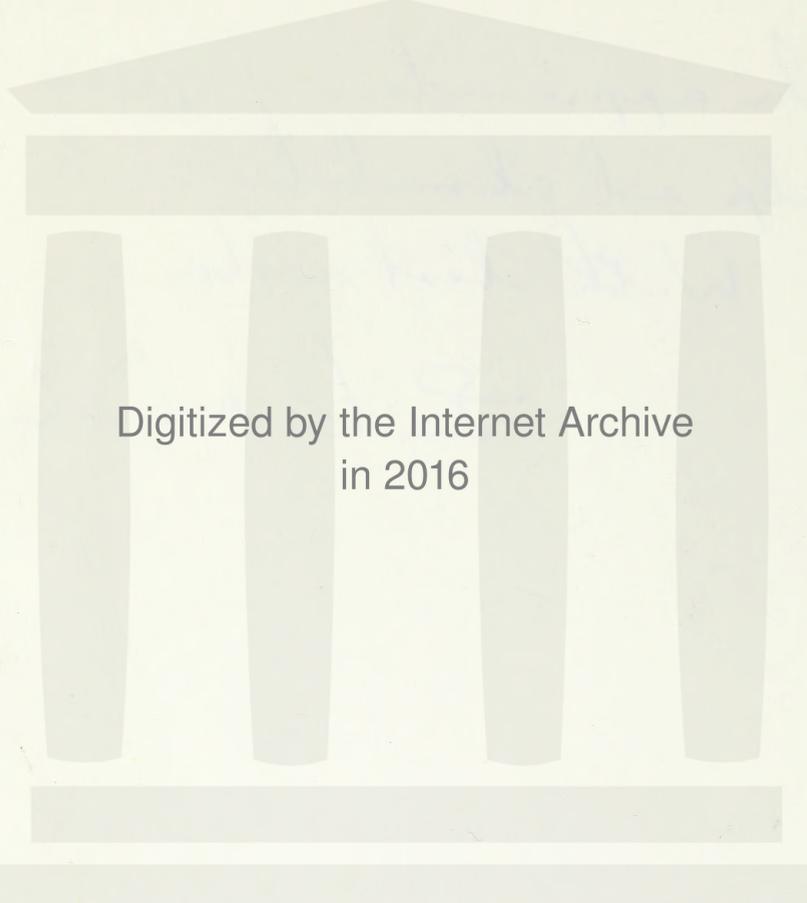




To Mark

In appreciation of your
help and stimulation,
With best wishes,

Ernie Register



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ORGANOMETALLICS IN ORGANIC SYNTHESIS

Volume One

Organometallics in Organic Synthesis

EI-ICHI NEGISHI

Purdue University

VOLUME ONE

General Discussions

Organometallics of Main Group Metals in Organic Synthesis

A WILEY-INTERSCIENCE PUBLICATION

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PREFACE

To Sumire

PREFACE

Since the discovery of the Grignard reagents at the turn of the century, the organometallic compounds have played a major role in organic synthesis both in academic laboratories and in industry. Today it is not only unwise but rather difficult to accomplish an efficient and selective multistep synthesis without using organometallics.

Despite wide-spread use of organometallics, there still exists a strong tendency to view organic chemistry as a branch of science dealing primarily with C, H, N, O, S, and halogens. Except for a few classes of organometallics, such as organolithiums and the Grignard reagents, the organometallics are often viewed as exotic. Persuaded by the literature that promises an attractive route to the desired compound, chemists occasionally use some organometallics with much hesitation. The results are often disappointing and frustrating. Poor results appear to stem, at least in part, from lack of sufficient knowledge of the scope and limitations of the procedure and of the proper handling of organometallics in such a procedure.

Another frequent problem is one of selecting the most suitable procedure for the desired transformation. For example, most elementary organic chemistry textbooks describe in some detail the addition reaction of Grignard reagents to ketones. The corresponding reaction of organolithium compounds, which often is far superior to the Grignard reaction, however, is seldom adequately discussed. Thus chemists are asked to learn this simple fact the hard way. Since the number of synthetic procedures to be exploited is increasing at a rapid pace, this difficulty is becoming increasingly serious. Some remedial measures must be provided.

Over the past decade or so a number of excellent textbooks (0.1 to 0.13)* and monographs (0.14 to 0.32) covering the general area of organometallic chemistry

*Reference numbers beginning with 0 are located in Appendix I, "General References," at the end of this volume.

have been published. Unfortunately, however, these discussions focus mostly on the preparation and structure of organometallic compounds themselves and/or the interconversion of organometallic substances. While teaching a course on organic synthesis at the graduate and undergraduate senior level, I saw the obvious need for a textbook or a supplementary textbook that would fill the gap between the more usual organic textbooks and organometallic textbooks. This book is written in response to that need.

The main objective of this book is to provide, in a concise form, a current overall picture of the chemistry of organometallics in organic synthesis. One way to accomplish such a task is to focus on a relatively small number of key features common to a large number of related reactions. While it may be ideal to classify various reactions according to mechanistic schemes, the present knowledge of organometallic reactions is not sufficiently developed to allow this approach. My discussion is therefore based primarily on the reactant-product relationship as well as on some tentative but reasonable interpretations provided both by the authors of individual papers and by myself. Such an approach is justified because (1) it is not inconsistent with experimental observations, (2) it helps to explain a large number of results (including even some that will be published in the future) in terms of a small number of common schemes, and, perhaps more importantly, (3) it provides some useful working hypotheses.

This is neither a reference book nor a comprehensive treatise. Thus the literature covered is highly selective. An effort has been made, however, to cite rather extensively reviews in which a number of pertinent original papers can be found. The following journals and review series provide the majority of reviews written in English in the area of organometallic chemistry.

Review Journals

1. *Acc. Chem. Res.*
2. *Angew. Chem. Int. Ed. Engl.*
3. *Chem. Rev.*
4. *Chem. Soc. Rev.*
5. *Intra-Sci. Chem. Rep.*
6. *J. Organometal. Chem.*
7. *Organometal. Chem. Rev. A*
8. *Pure Appl. Chem.*
9. *Quart. Rev.*
10. *Russ. Chem. Rev.*
11. *Synthesis*
12. *Tetrahedron Rep.*

Review Series

1. *Adv. Chem. Ser.*
2. *Adv. Inorg. Chem. Radiochem.*
3. *Adv. Org. Chem.*
4. *Adv. Organometal. Chem.*
5. *Org. React.*
6. *Organometal. React.*
7. *Progr. Inorg. Chem.*
8. *Top. Curr. Chem.*
(*Fortschr. Chem. Forsch.*)

In discussing works published in or before 1975 extensive use was made of various textbooks, monographs, and collections of reviews (Appendix I).

The nomenclature and terminology in organometallic chemistry are still quite underdeveloped and often inconsistent. Mainly for the sake of simplicity and consistency, I have decided to adopt certain unconventional names and terms. For example, tricoordinate and tetracoordinate organoboron compounds are called organoboranes and organoborates, respectively. There is, however, no simple name that applies to both. I suggest "organo + element + s" to describe collectively any organometallic compounds containing the element directly bonded to carbon regardless of their structural details. Thus both organoboranes and organoborates as well as subvalent organoboron compounds may be called *organoborons*. Organomercury compounds have traditionally been called organomercurials. The *al* ending, however, does not appear to have been used in any other class of organometallic compounds. Here again, the term *organomercuries* may be used to refer collectively to all types of organomercury compounds.

I wish to express my sincere appreciation to my former mentor, Professor Herbert C. Brown of Purdue University. His guidance, assistance, and influence have been essential in the writing of this book. I am directly and indirectly indebted to my colleagues in the Chemistry Department of Syracuse University. Occasional friendly reminders and assistance provided by Drs. Gershon Vincow and Daniel J. Macero are appreciated. I am deeply indebted to members of my research group, particularly Drs. Shigeru Baba, Anthony O. King, Ronald E. Merrill, Nobushisa Okukado, David E. Van Horn, and Takao Yoshida, who made significant contributions to our research activities. Among my current graduate students, I would especially like to thank Michael J. Idacavage, Louis F. Valente, and Cinthia L. Rand, not only for their research efforts, but for their help in preparing this manuscript. I would also like to mention the enjoyable and fruitful collaborative research efforts with Dr. Augustine Silveira, Jr. of the State University of New York at Oswego. I am grateful to a number of my colleagues in the field of organometallic chemistry for their helpful assistance. My thanks to Dr. Alan B. Levy of SUNY at Stony Brook, who read the entire manuscript and assisted in proofreading. Dr. Richard C. Larock of Iowa State University and Dr. Phillip L. Fuchs of Purdue University provided useful comments. Finally I would like to thank my wife, Sumire, for her direct and indirect assistance, including the typing of the entire manuscript, and Virginia Ditz, David Ditz, Diane Piraino and last but not least Roberta "Tooti" Molander for preparing the camera ready copy.

Ei-ichi Negishi

Syracuse, New York

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GENERAL DISCUSSIONS

**ORGANOMETALLICS
IN ORGANIC SYNTHESIS**

Volume One

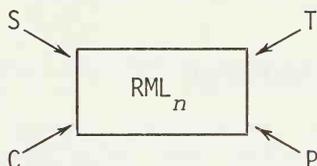
PART I

GENERAL DISCUSSIONS

1

SOME FUNDAMENTAL PROPERTIES OF METAL ATOMS, BOND TO METALS, CARBON GROUPS, AND ORGANOMETALLIC COMPOUNDS

The physical and chemical properties of organometallic compounds, which are the subjects of this book, must be governed by the properties of the metal (M) as well as organic (R) and inorganic (L) ligands. They must also be influenced by the environmental conditions, such as solvents (S), concentration (C), temperature (T), and pressure (P), in addition to the reagents with which they react.



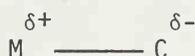
If we try to understand numerous organometallic reactions and attempt to predict some unknown but desirable organometallic reactions on at all a rational basis, it is essential to familiarize ourselves with some fundamental parameters affecting the properties of metals, organic and inorganic ligands, solvents, and so on. A detailed discussion of these parameters is beyond the scope of this book. The following brief discussion is intended merely to refresh our understanding of these parameters in order to establish a common platform for subsequent discussion. For more detailed treatment of the subject, the reader is referred to advanced textbooks (1.1 to 1.7).

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1.1 METAL ATOMS

1.1.1 Metals

The definition of the metallic elements is very nebulous at best. In our discussion, the metallic elements are those that can form bonds to carbon in which the carbon atom is negatively polarized, as in 1.1.



1.1

This requires that the electronegativity (EN) of the element in question be smaller than that of carbon, which has been arbitrarily set at 2.5 by Pauling (1.1). In practice, it is more convenient to limit the electronegativity range to ≤ 2.0 . Since there is no such thing as a truly reliable electronegativity value, our definition of the metallic elements is on precarious ground. Nonetheless, we adopt it mainly for the sake of convenience. As indicated in the Periodic Table (Appendix II), both boron (EN = 2.01) and silicon (EN = 1.74) are considered to be metallic elements here.

1.1.2 Electronic Configuration

Anyone who has taken an introductory course in chemistry knows that the elements within the same group behave similarly in many ways. This, of course, stems basically from the fact that they possess the same number of valence electrons. After all, the properties of elements, including their mutual similarities and differences, can in principle be explained in terms of the numbers of subatomic entities, that is, protons, neutrons, and electrons. These numbers are, of course, indicated by the atomic numbers and the atomic weights. Furthermore, these electrons are distributed among orbitals surrounding the atomic nuclei according to the aufbau principle based on the Pauli exclusion principle and Hund's rule. The distribution of the electrons of an atom is indicated by the electronic configuration (Appendix III). It is therefore highly advisable to familiarize ourselves with the electronic configurations of the elements of our concern.

1.1.3 Atomic Orbitals

Essential to our familiarization of the electronic configurations is our understanding of atomic orbitals, especially their shapes.

The approximate shapes of the s , p , and d orbitals with nodal signs are shown in Fig. 1.1.

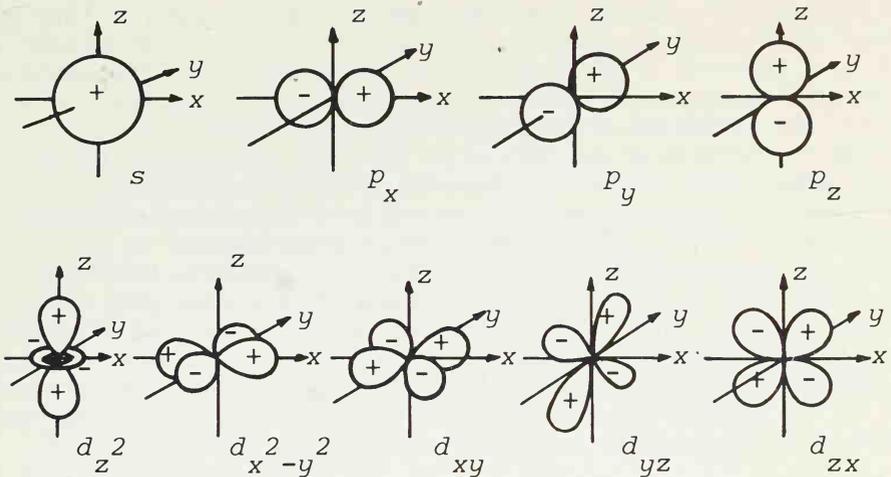
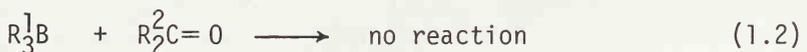
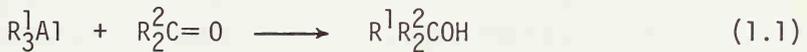


Fig. 1.1 Shapes of s , p , and d Atomic Orbitals

1.1.4 Electronegativity, Ionization Energy, Electron Affinity, and Atomic Size

Although the elements within the same group behave similarly in some ways, as stated earlier, they also behave very differently in many other ways. For example, whereas organoalanes (R_3Al) can react readily with aldehydes and ketones to form adducts, the corresponding organoboranes (R_3B) are generally inert under usual reaction conditions.



As will become clear in subsequent discussions, the differences among the elements of the same group often overshadow their similarities. As already mentioned, we should, in principle, be able to explain these differences in terms of the numbers of the subatomic components. It is generally more convenient, however, to discuss them in terms of more composite parameters which can be determined for each element, that is, electronic parameters,

such as electronegativity, ionization energy, and electron affinity, as well as parameters of size, such as covalent and ionic radii.

Electronegativity was first defined by Pauling (1.1) as the power of an atom in a molecule to attract electrons to itself. It is a property of an atom in a molecule under the influence of surrounding atoms. However, it has proven, in practice, to be useful to assign an electronegativity value to each element. Based on thermochemical data, Pauling first determined the electronegativities of various elements (1.1). Since then, a number of attempts have been made to devise an improved set of electronegativity values. Interested readers are referred to an excellent discussion by Huheey (1.3). For our purposes, however, it is sufficient to know only approximate electronegativity values. We arbitrarily choose Allred-Rochow values (1.8) as well as the original Pauling values (1.1 Appendix II). Allred and Rochow (1.8) defined electronegativity as the electrostatic force exerted by the nucleus on the valence electrons and obtained the formula

$$EN = 0.359z^*/r^2 + 0.744 \quad (1.3)$$

where z^* and r are the effective nuclear charge obtained by Slater's rules and the covalent radius, respectively. The Allred-Rochow and Pauling electronegativity values are very close to each other for most elements. Their values for most of the d block transition metals, however, are appreciably different from each other. Our current knowledge of these elements suggests that the Pauling values are much too high to be realistic. We will therefore be using mainly the Allred-Rochow values in these cases. In some other cases, EN of mercury, for example, neither the Allred-Rochow values nor the Pauling values appear to be realistic. Other values will therefore be considered in such cases.

It is useful to note that electronegativity increases as we ascend the Periodic Table within an A-subgroup or go from left to right among main group elements. The electronegativity values range from 0.7 (Pauling scale) for francium to approximately 4 for fluorine.[†] These values can now be used to estimate the direction of bond polarization, as discussed earlier, and the ionicity of a polarized bond, as discussed later.

Ionization energy (ionization potential) may be defined as the energy needed to remove an electron from an atom, that is,

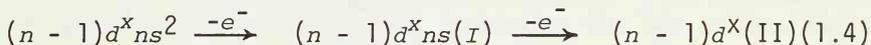
[†]The electronegativity of neon has been estimated at 5.1 by Allred and Rochow (1.8).

the energy difference between the highest occupied energy level and that corresponding to the complete removal ($n = \infty$). The ionization process is always endothermic. Thus, the ionization energy (IE) is always indicated by a positive value. The first four ionization energies for various elements are summarized in Appendix IV.

For the main group elements, the ionization energy tends to decrease as we descend within an A-subgroup due to the combined effects of size and shielding. As we go from left to right among main group elements, the effective nuclear charge (Z^*) increases, which tends to cause an increase in ionization energy.

As we go from Group IIA (s orbital) to Group IIIA (p orbital), however, we observe a decrease in ionization energy. This is due to the lower energy level of an s orbital relative to a p orbital of the same principal quantum number. The exchange energy between electrons of like spin stabilizes a system of parallel electron spins. This is responsible for the fact that the ionization energy of nitrogen is greater than that of oxygen.

The d -block transition atoms generally undergo the following ionization.



This provides an explanation for the fact that the +2 oxidation state is very common among transition elements.

Electron affinity (EA) is defined as the energy released when an electron is added to the valence shell of an atom. Note that a positive electron affinity value corresponds to a negative enthalpy value, and vice versa. While the definition of electron affinity is clear, its experimental determination has been difficult. As a result, only a limited number of electron affinity values are available. As might be expected, electron affinity trends more or less parallel those of ionization energies. According to Mulliken (1.9), electronegativity, ionization energy, and electron affinity are correlated according to the following equation:

$$EN = 0.168(IE_{VS} + EA_{VS} - 1.23) \quad (1.5)$$

where IE_{VS} and EA_{VS} are valence state values in electronvolts.

Atomic size is another nebulous quantity associated with a given atom, and is very much dependent on the conditions under which the atom exists. It is, however, useful to discuss the following notable trends in atomic sizes.

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1. Atomic sizes tend to increase, as we descend within the same group.
2. Atomic sizes decrease, as we go from left to right within a given series. It follows that a sudden increase in atomic size occurs, as we go from an inert gas to an alkali metal with the next higher atomic number.

In order to discuss atomic sizes in a quantitative manner, we must know the nature of the bonds formed by the atoms of our concern. Various types of atomic radii will be described in our discussion of bonds to metals in the following section.

1.2 BONDS TO METALS

1.2.1 Covalent Bond Versus Ionic Bond

Covalent bonds and ionic bonds are two representative chemical bonds. Although it is not our intention to discuss here any quantum mechanical theory of these chemical bonds, it is useful to review briefly the relation between the atomic properties discussed above and the nature of the chemical bond. A bond formed between two like atoms, for example, an H-H bond, may be viewed as being essentially covalent. On the other hand, there is no such thing as a 100% ionic bond. Thus all bonds between two or more unlike atoms are partially ionic and partially covalent.

Ionicity of a bond between two unlike atoms, A and B, is primarily governed by the difference between the electronegativity values of the two atoms. Pauling (1.1) proposed the following equation to estimate the percent ionicity of a bond between atoms A and B (Table 1.1).

$$\text{Ionicity (\%)} = 1 - e^{-\frac{1}{4}(EN_A - EN_B)} \quad (1.6)$$

If we use this equation, we find that the bond between B (EN = 2.0) and C (EN = 2.5) is only approximately 6% ionic. Even the Cs-C bond, which is regarded as one of the most ionic metal-carbon bonds, is only approximately 50% ionic. We are not in a position to critically evaluate the validity of the above estimations. Furthermore, we do know that the ionicity of the metal-carbon bond is greatly affected by the nature of the carbon group, as discussed later. Nonetheless, it is important to realize that most of the metal-carbon bonds that concern us are likely to be relatively covalent.

Table 1.1 Relation Between Electronegativity Difference and Ionicity of Single Bonds

$EN_A - EN_B$	Ionicity(%)	$EN_A - EN_B$	Ionicity(%)
0.2	1	1.8	55
0.4	4	2.0	63
0.6	9	2.2	70
0.8	15	2.4	76
1.0	22	2.6	82
1.2	30	2.8	86
1.4	39	3.0	89
1.6	47	3.2	92

Although it is generally difficult to correlate the ionicity of a bond with some measurable quantities, the ionicity (q) of a diatomic molecule can readily be estimated from its bond length (r) and gas-phase dipole moment (μ) according to eq. 1.7.

$$q = \frac{\mu(D) \times 10^{-18} \text{ \AA-esu}}{r \text{ \AA} \times 4.8 \times 10^{-18} \text{ esu}} \quad (1.7)$$

1.2.2 Polarizability

A common misconception is to think that a highly covalent bond is very reluctant to participate in ionic reactions. We all know that the essentially covalent iodine molecule readily participates in a variety of ionic reactions. This is qualitatively explained in terms of the high polarizability of the iodine-iodine bond. Polarizability is yet another highly nebulous property that is a function of a number of factors including the shape, size, and other properties of the bond-forming orbitals. Whereas the ionicity of a bond is related to its permanent bond dipole moment, the polarizability of a bond is related to its induced bond dipole moment. Despite the vagueness of our current understanding, however, the concept of polarizability is of essential importance in our discussion of the chemistry of organometallic compounds containing heavy atoms, such as Hg, Tl, and Pd.

1.2.3 Bond Strength and Bond Length

In addition to polarity and polarizability, bond strength and bond length are important parameters of any bond affecting the kinetics and thermodynamics of the reactions in which the bond in

question participates.

Covalent Bond Energies and Covalent Bond Lengths The energy required to cleave a covalent bond to give the constituent radicals is called the bond dissociation energy (DE). Although its definition is clear, its measurement is often difficult. Consequently, a more ambiguous but more readily obtainable quantity termed "bond energy" has been introduced. This corresponds to the average of the bond dissociation energies for all bonds of one kind present in a given molecule. In our discussions, we will be primarily dealing with bond energies (BE). The metal-carbon bond energies for some relatively covalent organometallic compounds of the Me_nM type are listed in Table 1.2.

Table 1.2 Metal-Carbon Bond Energy for Me_nM

Me_2M	BE (kcal/mole)	Me_3M	Be (kcal/mole)	Me_4M	BE (kcal/mole)
Me_2Be	-	Me_3B	87	Me_4C	83
Me_2Mg	-	Me_3Al	66	Me_4Si	70
Me_2Zn	42	Me_3Ga	59	Me_4Ge	59
Me_2Cd	33	Me_3In	-	Me_4Sn	52
Me_2Hg	29	Me_3Tl	-	Me_4Pb	37

A large number of bond energy and bond length values have been compiled by Cottrell (1.10).

The covalent bond length can be determined accurately by X-ray analysis and microwave spectroscopy. It is, however, useful to be able to estimate the bond length ($r_{\text{A-B}}$) between atoms A and B from their atomic parameters, termed covalent radii (r_{COV}). If we can determine the covalent bond lengths ($r_{\text{A-A}}$) of homonuclear bonds, the covalent radii (r_{A}) can be obtained by dividing them by two. If not, some indirect methods must be used. Schomaker and Stevenson (1.11) proposed the following relation:

$$r_{\text{A-B}} = r_{\text{A}} + r_{\text{B}} - 0.09 (|\text{EN}_{\text{A}} - \text{EN}_{\text{B}}|) \quad (1.8)$$

Equation 1.8 can be used to estimate r_{A} from the heteronuclear bond length ($r_{\text{A-B}}$), the covalent radius of atom B (r_{B}), and the electronegativity difference ($|\text{EN}_{\text{A}} - \text{EN}_{\text{B}}|$). This equation suggests that for highly covalent bonds the covalent atomic radii

are reasonably additive. The covalent radii for various elements are listed in Appendix V.

Lattice Energy and Ionic Radii The energy of the crystal lattice of an ionic compound is represented by the lattice energy, which can be determined experimentally. Although the distances between two neighboring cations and anions in ionic crystals can be measured with a high degree of accuracy, it is difficult to correctly apportion them between the cations and the anions. Many devices have been designed for this purpose. For our discussions, it will suffice to know general trends in ionic radii and their approximate values (Appendix V).

1.3 CARBON GROUPS

1.3.1 Electronegativity and Basicity of Carbon Groups and Acidity of Carbon Acids

One of the most important properties associated with the organic moiety (R) of an organometallic compound is its basicity. Since the basicity of R is significantly modified by the metal-containing moiety, it is more convenient to discuss the acidity (pK_a) of the conjugate carbon acid (RH), which is a parameter representing the electronegativity of the R group. Detailed discussions of this subject have been presented in many excellent monographs (1.12 to 1.16). We shall briefly touch on some factors affecting the acidity of carbon acids. The pK_a values of some representative carbon acids are summarized in Appendix VI.

1.3.1.1 Inductive Effect Due to Hetero Atoms

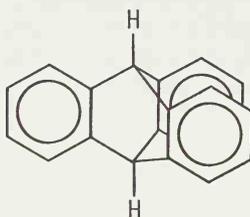
The pK_a values for methane and chloroform are 48 and 24, respectively. This difference is readily explained in terms of the electron-withdrawing inductive effect of the highly electronegative Cl atom.

1.3.1.2 Resonance Effect and Resonance Inhibition

The resonance effect on the acidity of carbon acids is clearly seen in the pK_a values of a series of phenylated methans: PhCH_3 ($pK_a = 41$), Ph_2CH_2 ($pK_a = 34$), and Ph_3CH ($pK_a = 31-32$). The markedly higher acidity of toluene relative to that of methane is largely due to the extensively delocalized nature of the corresponding benzyl carbanion. The acidity of diphenylmethane can be interpreted in an analogous manner. On the other hand, the intro-

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duction of the third phenyl group has a much smaller effect than that of the first or second. This has been interpreted in terms of steric inhibition of resonance due to the propeller-shaped structure of the trityl anion. This explanation is plausible, as triptycene (1.2), whose benzylic carbanion cannot be stabilized through delocalization, is indeed a considerably weaker acid (pK_a 42) than triphenylmethane.



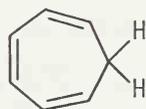
1.2

1.3.1.3 Aromaticity

The relative pK_a values of cyclopentadiene and cycloheptatriene cannot be explained in terms of the extent of delocalization alone. The aromaticity ($4n + 2$ electrons) and anti-aromaticity ($4n$ electrons) of these carbanions must also be taken into consideration.



($pK_a = 15$)



($pK_a = 36$)

1.3.1.4 Hybridization Effect

The pK_a values of ethane ($pK_a = 49$), ethylene ($pK_a = 44$), and acetylene ($pK_a = 25$) can be interpreted in terms of the differences in hybridization. The $2s$ atomic orbital energy level is lower than that of the $2p$ orbital. Thus, electrons are closer and more tightly bound to the nucleus in the $2s$ orbital than in the $2p$ orbital. In other words, the $2s$ orbital is more electronegative than the $2p$ orbital. The electronegativity order for sp hybrid orbitals as well as s and p orbitals is $s > sp > sp^2 > sp^3 > p$.

1.3.2 Bond Energies and Bond Lengths of Some Carbon-Carbon and Carbon Hetero Atom Bonds

In the preceding section, we considered only one bond energy value and one bond length value for a given bond (A-B). This, of course, is a gross oversimplification. We do know that the bond between two given atoms A and B can be significantly affected by neighboring and surrounding atoms, groups, molecules, and so on. While this must be true with all types of bonds, we shall consider only the hybridization effect on the carbon-carbon and some carbon-hetero atom (nonmetal) bond lengths as one of the most noticeable and significant examples.

Table 1.3 lists some carbon-carbon and carbon-hetero atom bond lengths. The pronounced effect of bond multiplicity is readily understood.

Table 1.3 Bond Lengths of Some Carbon-Carbon and Carbon-Hetero Atom Bonds

Bond Type	Length (Å)	Bond Type	Length (Å)
C-C		C-H	
sp^3-sp^3	1.54	$sp^3, sp^2, \text{ or } sp\text{-H}$	1.10 ± 0.02
sp^3-sp^2	1.50	C-N	
sp^3-sp	1.46	$sp^3\text{-N}$	1.47
sp^2-sp^2	1.48	$sp^2\text{-N}$	1.36
sp^2-sp	1.43	C=N	
$sp-sp$	1.38	$sp^2\text{-N}$	1.28
C=C		C≡N	
sp^2-sp^2	1.34	$sp\text{-N}$	1.16
sp^2-sp	1.31	C-O	
$sp-sp$	1.28	$sp^3\text{-O}$	1.41
C≡C		$sp^2\text{-O}$	1.34
$sp-sp$	1.21	C=O	
		$sp^2\text{-O}$	1.20
		$sp\text{-O}$	1.16

The effect of hybridization has been interpreted in terms of partially increased bond multiplicity due to resonance and hyperconjugation, as indicated below.



These effects are also seen in the bond energies of these bonds. However, as we have already discussed earlier, the bond energy is a less well-defined parameter than the bond length. To indicate the effect of bond multiplicity, some bond energy data are shown in Table 1.4.

Table 1.4 Bond Energies for Some Carbon-Carbon and Carbon-Hetero Atom Bonds

Bond	Bond Energy (kcal/mole)	Bond	Bond Energy (kcal/mole)
C-C	83-85	C-O	85-91
C=C	146-151	C=O	173-181
C≡C	199-200	C-S	66
C-H	96-99	C-Cl	79
C-N	69-75	C-Br	66
C=N	143	C-I	52
C≡N	204		

1.4 MOLECULAR STRUCTURE

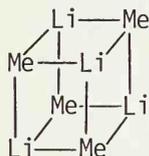
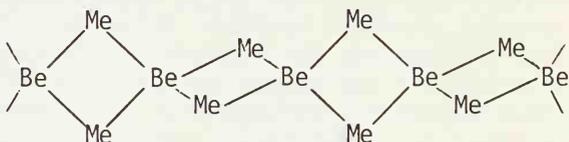
We have so far discussed some of the important atomic and bond parameters without dealing with the overall molecular shapes or structures. In this section, let us briefly review some factors governing (1) the elemental composition and the topology, that is, the atom-linking sequence and then (2) the three-dimensional molecular shape, without resorting to sophisticated modern quantum mechanical theories. For more rigorous and sophisticated treatments, the reader is referred to some of the textbooks and monographs cited earlier (1.1 to 1.7).

1.4.1 The Lewis Octet Rule

Despite the development of many sophisticated theories, the simple empirical rule of bonding developed by Lewis, called the Lewis octet rule, still provides a convenient basis for understanding and predicting molecular structures containing many im-

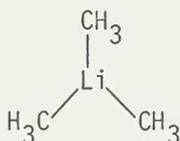
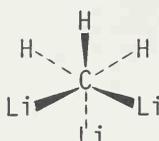
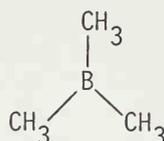
portant main group elements. It simply states that the first-row atoms have a strong tendency to acquire eight valence electrons, which the inert gas atom of the same row, namely neon, has. We all know that we must apply the modified "two-electron rule" to hydrogen and helium and that hypervalency or valence-shell expansion can be observed with heavier atoms. In dealing with *d*-block transition metals, the 16 or 18 electron rules discussed in Sect. 8.1 have proved useful.

The application of the Lewis octet rule to the organometallic compounds of the main group metals requires special comments. If we examine the monomeric representations of LiMe , BeMe_2 , and BMe_3 , we find that none of them is in accord with the octet rule. They are a duet, a quartet, and a sextet, respectively. In light of the low ionicity of the metal-carbon bonds of these compounds, the ionic representations, such as $\text{Be}^{+2}\text{Me}_2^{-1}$, which would be in agreement with the octet and two-electron rules, cannot be significant. Consequently, if the Lewis octet rule were at all meaningful in such cases, it must imply either that these molecules do not exist as monomers or that they have a strong tendency to accept electrons so as to acquire a total of eight valence electrons. As discussed in Sect. 4.1, LiMe indeed exists as its tetramer 1.3, and BeMe_2 as its polymer 1.4.

1.31.4

As discussed later in more detail the metal atoms in these compounds are bonded to the methyl groups via multicenter bonding. Each lithium atom is simultaneously bonded to three methyl groups, as shown in 1.5, and each methyl group is simultaneously bonded to three lithium atoms, as shown in 1.6. Only BMe_3 appears to exist as a monomeric species under normal conditions. In a formal sense, the Li atom in $(\text{LiMe})_4$ and the B atom in BMe_3 are sextets, and the Be atom in $(\text{BeMe}_2)_n$ an octet. Moreover, these electron-deficient species, BMe_3 , for example, have a strong tendency to acquire electrons, that is, Lewis acidic, so as to form Lewis octets through either self-association or com-

plexation with electron donors (Lewis bases). In conclusion, then, many commonly employed monomeric representations of organometallic compounds of the main group metals do not obey the Lewis octet rule. However, they either exist as octet species through association or display properties, which can be readily explained within the context of the Lewis octet rule.

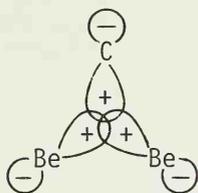
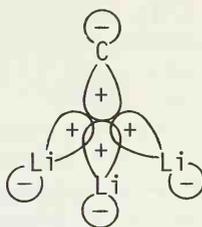
1.51.61.7

1.4.2 Coordinative Saturation and Unsaturation and Multicenter Bonds

Electron-deficient species, such as BMe_3 , are said to be coordinatively unsaturated, since there is at least one empty valence orbital available for extra coordination or bond formation. Conversely, chemical species, in which all valence orbitals are doubly occupied, are coordinatively saturated. As previously indicated, a large number of organometallic compounds are either coordinatively unsaturated or capable of generating coordinatively unsaturated species. This is not the case with organic compounds, which do not contain metals. Organic compounds rarely exist as coordinatively unsaturated stable species. Carbonium ions and singlet carbenes are coordinatively unsaturated, but they are usually very short-lived. On the other hand, most triorganoboranes exist as thermally stable sextets. Similarly, diorganoberylliums and triorganoalanes contain thermally stable monomeric species in the vapor phase.

One of the characteristics of these coordinatively unsaturated species is their tendency toward self-association, as mentioned earlier. This association phenomenon should clearly be separated from other much weaker intermolecular association phenomena, such as the association of coordinatively saturated covalent molecules through very weak London forces. The metal-carbon and metal-hetero atom bonds that are responsible for forming associated organometallic species are conveniently described in terms of multicenter two-electron bonds, originally proposed by

Longuet-Higgins (1.17) for explaining the structure of diborane. Thus, the Be-C-Be bond in $(\text{BeMe}_2)_n$ is a three-center two-electron bond represented by 1.8, and the Li atom of $(\text{LiMe})_4$ participates in a four-center two-electron bond represented by 1.9. Only the bonding orbitals are shown.

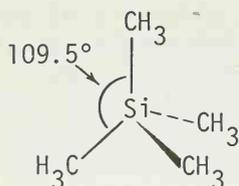
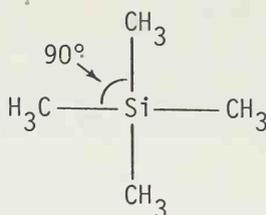
1.81.9

Note that the carbon atoms of $(\text{BeMe}_2)_n$ and $(\text{LiMe})_4$ are pentavalent and hexavalent, respectively. The familiar but naive concept of tetravalency for carbon must be abandoned in describing these multicenter bonds. What we do not have to discard is the Lewis octet rule. It should be clearly recognized that, despite their "abnormal" valencies, the carbon atoms of $(\text{BeMe}_2)_n$ and $(\text{LiMe})_4$ are all octets. The significance of the concept of multicenter bond in organometallic chemistry cannot be overemphasized. Unfortunately, a detailed description of multicenter bonds is beyond the scope of our discussion. Interested readers are referred to advanced textbooks and reviews discussing this subject, such as those by Cotton (1.7) and Lipscomb (1.18).

1.4.3 Parameters Governing Molecular Shapes - Bond Angle, Hybridization, and Electron-Electron Repulsion

Although the Lewis octet rule is useful in understanding and predicting the atom-linking sequence in a molecule, it does not predict or help us understand the three-dimensional structure of the molecule, except in some very simple cases, such as diatomic molecules. For example, the Lewis octet rule itself does not distinguish 1.10 from 1.11.

Experimentally, what we need to know are some bond angles in the molecule and information on some dynamic aspects of the molecule. Thus if we know the C-Si-C, H-C-H, and Si-C-H bond angles and the freely rotating nature of the Si-C bond in addition to

1.101.11

the atom-linking sequence, we can unequivocally establish the three-dimensional structure of $\text{Si}(\text{CH}_3)_4$. X-ray and electron diffraction methods have been widely used for the determination of bond angles. The dynamic properties of molecules have been studied using various spectroscopic methods including NMR.

The concept of hybrid orbitals helps explain molecular shapes. Thus the tetrahedral arrangement about the Si atom of SiMe_4 is readily explained in terms of the sp^3 hybridization of the Si valence orbitals. The bond angles associated with some common hybridizations are summarized in Table 1.5.

Table 1.5 Relation Between Hybridization and Bond Angles

Hybridization	Bond Angle(s)	Hybridization	Bond Angle(s)
sp	180°	dsp^2	90°
sp^2	120°	dsp^3	90° and 120°
sp^3	109.5°	d^2sp^3	90°

It should be emphasized, however, that it is not hybridization that dictates the three-dimensional structure. In fact, the bond angles listed in Table 1.5 are observed only with atoms that are bonded to one type of atoms or groups. In the other cases, the bond angles usually deviate from these listed values. It is the energetics of a molecule that determine its three-dimensional structure. In other words, with a given topology or atom-linking sequence, a molecule will shape itself up in three-dimensional space so as to minimize its potential energy.

What then controls the energy of a molecule with a given atom-linking sequence? While there can be various factors governing the bond angles or three-dimensional shape of a molecule, the

principal factor is presumably an electron-electron repulsion force. Three types of electron-electron repulsions that must be considered are: lone pair-lone pair > lone pair-bonding pair > bonding pair-bonding pair. The order of the magnitude of repulsion energies is as indicated above (1.19). Although such a crude and qualitative theory does not give precise bond angles, it will permit us to predict the overall structure of a molecule and the approximate bond angles with reasonable confidence. The trigonal planar arrangement for the B atom of BMe_3 , the pseudo tetrahedral arrangement for the Be atoms of $(\text{BeMe}_2)_n$ and the tetrahedral arrangement for the Si atom of SiMe_4 can readily be predicted based on the electron-electron repulsion theory presented above. In addition to the papers by Gillespie (1.19), Huheey provides a detailed discussion of this subject in his textbook (1.3).

1.5 INTERMOLECULAR FORCES

Highly covalent organic molecules are held together in liquid and solid phases by weak van der Waals forces, such as London dispersion force, and the intermolecular distances are represented by van der Waals radii. The relation between the covalent and van der Waals radii in homonuclear diatomic molecules is shown in Fig. 1.2.

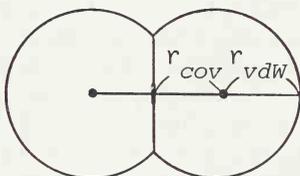


Fig. 1.2 The relation between the covalent and van der Waals radii

As the ionicity of a bond increases, stronger electrostatic interactions, such as hydrogen bonding, solvation, inclusion, charge-transfer complex formation, and so on, become more and more important. These interactions are often largely electro-

static in nature and can be classified into dipole-dipole, pole(ion)-dipole, and pole(ion)-pole(ion) interactions. Even in these intermolecular interactions, however, orbital-orbital interaction, that is, covalent bonding, often plays a significant role. Moreover if we consider all types of intermolecular interactions, we soon recognize that it is impossible to classify all chemical bonds into two distinct classes, that is, intramolecular and intermolecular bonds. It is neither appropriate nor necessary to discuss all these different types of intermolecular bondings here.

It is very important, however, to fully realize that both the relatively high polarity of the metal-carbon bonds and the wide occurrence of coordinatively unsaturated organometallic species, as well as self-associated organometallic species, make intermolecular interactions that are stronger than van der Waals interactions widely observed and highly significant in organometallic chemistry. As a typical and significant example, consider solvation. The process of dissolving typical organic compounds, such as cyclohexanone, in a typical organic solvent, such as tetrahydrofuran (THF), is normally associated with weak electrostatic interactions. The IR carbonyl stretching frequency, for example, is only slightly affected by solvation. On the other hand, the process of dissolving organometallic compounds in organic solvents, such as THF, is often accompanied by much stronger interactions. For example, $(\text{AlMe}_3)_2$, a self-associated dimeric species, undergoes dissociation and forms a relatively stable 1:1 complex, that is, $\text{AlMe}_3 \cdot \text{THF}$, which gives totally different spectral data than $(\text{AlMe}_3)_2$. In other words, THF is acting as both a solvent and a reactant. In trying to understand and predict the course of an organometallic reaction, it is often of essential significance to consider the "solvent" as a reagent or reactant. For example, if we compare the rates of hydroboration of typical olefins, such as ethylene, with BH_3 and ClBH_2 , we obtain the following results. In THF, the reaction is much faster with BH_3 than with ClBH_2 , whereas the opposite is the case in ethyl ether. A priori, one might predict that the stronger Lewis acid of the two, that is, ClBH_2 , would be the more reactive of the two. That is what one finds in ethyl ether, irrespective of their precise structures. In THF, however, their reactivity order is reversed, because the stronger Lewis acid, ClBH_2 , forms a much tighter complex with THF than BH_3 . In short, it is advisable to consider any solvents of electron-donating ability as reagents. For more systematic discussions of intermolecular interactions, the reader is referred to some of the textbooks cited earlier (1.1 to 1.3).

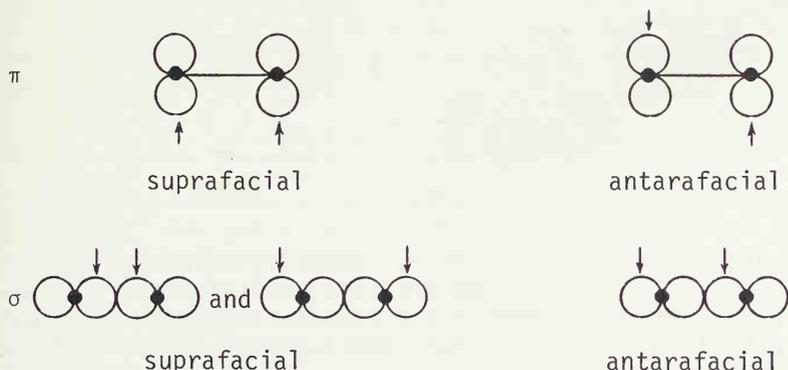
1.6 SOME FACTORS CONTROLLING CHEMICAL REACTIONS

Chemical reactions, including all organometallic reactions, may be arbitrarily classified into the following three general types: (1) generalized acid-base or electrophile-nucleophile reactions, that is, polar reactions, (2) free-radical reactions, and (3) concerted molecular reactions, which do not correspond to either (1) or (2), that is, pericyclic reactions. Within the past two decades, significant advances have been made in our understanding of the polar and pericyclic reactions. Especially noteworthy are the principle of conservation of orbital symmetry developed by Woodward and Hoffmann, called the Woodward-Hoffmann rule (1.6), and the principle of the hard and soft acids and bases (the HSAB principle) developed by Pearson (1.20), which has been significantly reinforced by Klopman's perturbation treatment (1.21). There are many excellent reviews on both the Woodward-Hoffmann rule and related theories (1.5, 1.6, 1.22 to 1.25) and the HSAB principle (1.20, 1.25). Consequently, it will suffice to present a very brief description of these principles and a few comments pertaining to their use in organometallic chemistry.

1.6.1 The Principle of Conservation of Orbital Symmetry

Based on the principle that orbital symmetry is conserved in concerted reactions, Woodward and Hoffmann (1.6) presented the following general rule for pericyclic reactions.

A ground-state or thermal reaction is symmetry allowed if the total number (Σ) of ($4q + 2$) suprafacial and $4r$ antarafacial components is odd (q and $r = 0$ or integers). The number of electrons involved in each component is indicated by either $4q + 2$ or $4r$. The reverse would be true for excited-state or photochemical reactions. The suprafacial and antarafacial modes of interactions are shown below for π , σ , and ω (nonbonding) orbitals.



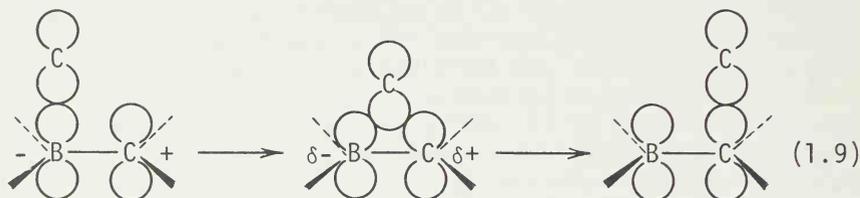


suprafacial



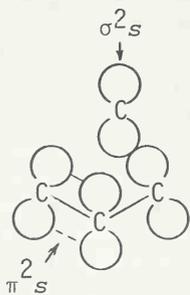
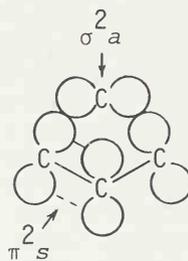
antarafacial

For example, the 1,2-migration reactions of organoboranes via organoborate intermediates discussed in Sect. 5.2.3 is a $[\sigma^2_s + \omega^0_s]$ process ($\Sigma = 1$) which is thermally allowed and should proceed with retention of configuration of the migrating group.



(1.9)

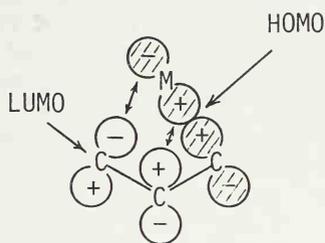
If one starts applying the Woodward-Hoffmann rule to organometallic reactions one soon recognizes that many organometallic reactions, which appear to be concerted, proceed readily under thermal conditions, and must therefore be thermally allowed, even when their organic counterparts do not occur readily. For example, the 1,3-shift or allylic rearrangement of an alkyl group (R) does not occur readily, presumably because the low strain process represented by 1.12 is a thermally disallowed $[\pi^2_s + \sigma^2_s]$ process ($\Sigma = 2$), whereas the thermally allowed $[\pi^2_s + \sigma^2_a]$ process represented by 1.13 is a high strain process.

1.121.13

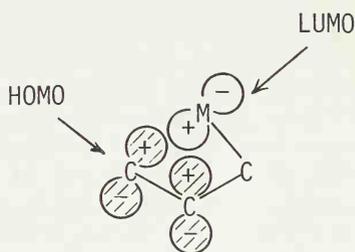
On the other hand, a number of 1,3-metallotropic reactions are very facile, we further notice that the metal atoms of facile 1,3-metallotropic reactions either are coordinatively unsaturated or can readily be converted into coordinatively unsaturated atoms.

Indeed, many other seemingly concerted facile organometallic reactions, which might at first sight appear thermally disallowed by the principle of orbital symmetry conservation, are associated with the presence of an empty metal orbital. A wide variety of cis hydrometallation and carbometallation reactions fall into this category. The effect of an empty metal orbital can be explained most conveniently by Fukui's frontier orbital theory (1.22).

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) are called the frontier orbitals, which may be loosely equated to the filled and empty valence orbitals of atoms. If the symmetry of the HOMO of one reactant or component is such that it can overlap with the LUMO of the other reactant or component, the reaction between the two reactants or components is favored as a concerted process. The HOMO-LUMO interactions in the 1,3-metallotropy are shown in 1.14 and 1.15.



1.14



1.15

The interaction in 1.14 is equivalent to the $[\pi 2_s + \sigma 2_a]$ interaction shown in 1.13. Therefore, it appears the HOMO-LUMO interaction shown in 1.15 is mainly responsible for the ease with which the coordinatively unsaturated allylmetals undergo the 1,3-shift.

1.6.2 The Principle of Hard and Soft Acids and Bases

The Woodward-Hoffmann rule, which deals only with the symmetry aspects of orbitals, is a very rigid theory that has been successfully applied to most, if not all, of the pericyclic reactions. Its main limitation is that it cannot be applied to other types of reactions. Although no comparable theory that is applicable to other types of reactions has been developed, a more widely applicable but much more "soft" principle of the hard and

soft acids and bases (1.20) has proved to be highly useful.

In Klopman's quantum mechanical treatment (1.21), energy change (ΔE) in a chemical reaction is evaluated in terms of a charge-charge interaction representing electrostatic interactions, an orbital-orbital interaction, and a solvation shown in eq. 1.10

$$\Delta E = \frac{-q_R q_S e^2}{d\epsilon} + \sum_m \sum_n \left[\frac{2(C_R^m)^2 (C_S^n)^2 \beta^2}{E_m^* - E_n^*} \right] + \Delta_{\text{Solv}} \quad (1.10)$$

occ. unocc.

where q_R and q_S are charges of the reactants R and S , respectively, d is the distance between these sites, ϵ is the dielectric constant, C_R^m , C_S^n are the coefficients of the atomic orbital x in a frontier orbital m of energy E_m^* and of the atomic orbital s in a frontier orbital n of energy E_n^* , respectively, β is the resonance integral of the developing bond, $E_m^* - E_n^*$ is the energy difference of the frontier orbitals m and n , and Δ_{Solv} is solvation energy. When the difference in energy between the frontier orbitals is large, the second term in eq. 1.10 is small, and the reaction is dominated by electrostatic interactions and is said to be charge controlled. When $|E_m^* - E_n^*|$ is small, the interactions are primarily covalent, and the reaction is said to be frontier controlled. A charge-controlled reaction is favored by species of small size and of low polarizability with high effective nuclear charge. Acids (electrophiles) and bases (nucleophiles) that have these properties are called "hard" acids and "hard" bases. On the other hand, the frontier-controlled reaction is favored by large, highly polarizable species of low or zero nuclear charge. These species are called "soft" acids and "soft" bases. The HSAB principle clearly indicates that it is intrinsically incorrect to relate a reaction rate to a particular reactivity index of a reactant. Thus there can be no such thing as the universal nucleophilicity or electrophilicity order. The relation between the ease of reaction and the hardness or softness of the acids and bases is shown in Table 1.6.

More than 20 years ago, Chatt (1.26) classified various metal ions and ligand bases into two classes, which correspond to Pearson's hard and soft species. The abilities of various ligand bases to complex with hard metal ions, such as Al^{+3} , Ti^{+4} , and Co^{+3} , and with soft metal ions, such as Pt^{+2} , Ag^+ , and Hg^{+2} , are shown in Table 1.7. Only the atoms acting as a basic center are indicated.

Table 1.6 Rates of Reactions between Hard and Soft Reagents

Acid	Base	$ E_m^* - E_n^* $	e^2/d	β	Rate
Hard	Hard	Large	Large	Small	High
Soft	Soft	Small	Very small	Large	High
Hard	Soft	Medium	Small	Very small	Low
Soft	Hard	Medium	Small	Very small	Low

Table 1.7 The Ability of Bases to Complex with Metal Ions

Ability to Complex with Hard Metal Ions	Ability to Complex with Soft Metal Ions
N >> P > As > Sb	N << P > As > Sb
O >> S > Se > Te	O << S < Se ~ Te
F > Cl > Br > I	F < Cl < Br < I

Table 1.8 Classification of Bases^a

Hard Bases	NH ₃ , RNH ₂ , NH ₂ NH ₂ H ₂ O (-10.73), ⁻ OH (-10.45), HOR, ⁻ OR, OR ₂ ⁻ OAc, CO ₃ ⁻² , NO ₃ ⁻ , PO ₄ ⁻³ , SO ₄ ⁻² , ClO ₄ ⁻ F ⁻ (-12.18), Cl ⁻ (-9.94)
Borderline Bases	ArNH ₂ , C ₅ H ₅ N, N ₂ , N ₃ ⁻ NO ₂ ⁻ , SO ₃ ⁻ Br ⁻ (-9.22)
Soft Bases	H ⁻ (-7.37) R ⁻ , olefin, arene, C≡O, CN ⁻ (-8.78), RNC PR ₃ , P(OR) ₃ , AsR ₃ HSR, ⁻ SR, ⁻ SH (-8.59), SR ₂ , S ₂ O ₃ ⁻² I ⁻ (-8.31)

^a The numbers in parentheses are Klopman's softness parameters (E^{\ddagger}) in electronvolts.

Table 1.9 Classification of Metal Ions (Softness Parameter S^{\ddagger} , eV)

Some Hard Main Group Metal Ions

H^+ (0.42)			
Li^+ (0.49)	Be^{+2} (3.75)	B^{+3}	
Na^+ (0.00)	Mg^{+2} (2.42)	Al^{+3} (6.01)	Si^{+4}
K^+	Ca^{+2} (2.33)	Ga^{+3} (1.45)	Ge^{+4}
Rb^+	Sr^{+2} (2.21)		Sn^{+4}
Cs^+	Ba^{+2} (1.89)		

Some Hard Transition Metal Ions

Sc^{+3}	Ti^{+4} (4.35)	V^{+3}	Cr^{+3}	Mn^{+2}	Fe^{+3}	Co^{+3}
				$^{+6}$		
	Zr^{+4}		Mo^{+4}			
	Hf^{+4}		W^{+4}			
La^{+3} (4.51)						

Some Soft and Borderline Metal Ions

Borderline Acids (Transition Metal Ions)

Fe^{+2}	Co^{+2}	Ni^{+2}	Cu^{+2}	Zn^{+2}
Ru^{+2}	Rh^{+3}	Pd^{+2}	Cu^+	Ag^+ (-2.82)
Os^{+2}	Ir^{+3}	Pt^{+4}	Au^+ (-4.35)	Hg^{+2} (-4.64)
				Tl^{+3} (-3.37)

↑
Soft Acids

Borderline Acids (Main Group Metal Ions)

Sn^{+2}	Sb^{+3}
Pb^{+2}	Bi^{+3}

Table 1.10 Classification of Acids Other than Metal Ions

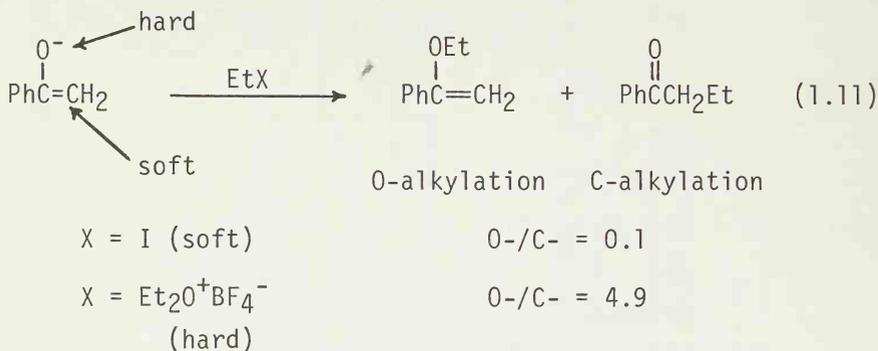
Hard Acids	BF ₃ , BCl ₃ , B(OR) ₃ , AlH ₃ , AlR ₃ , AlCl ₃ RCO ⁺ , CO ₂ N ⁺³ , As ⁺³ , SO ₃ , RSO ₂ ⁺ , Cl ⁺³ , Cl ⁺⁷ , I ⁺⁵ , I ⁺⁷
Borderline Acids	BR ₃ , GaH ₃ R ₃ C ⁺ , Ph ⁺ NO ⁺ , SO ₂
Soft Acids	BH ₃ , GaR ₃ , TlR ₃ CH ₂ Quinones, (NC) ₂ C=C(CN) ₂ HO ⁺ , RO ⁺ , RS ⁺ , Br ₂ , Br ⁺ , I ₂ , I ⁺ , ICN Cl·, Br·, I·, RO·, RO ₂ · Metal atoms and bulk metals

Pearson (1.20) has expanded this concept and classified qualitatively a variety of acids and bases according to their hardness or softness (Tables 1.8 to 1.10). Klopman introduced a parameter E^\ddagger , which is a measure of softness, based on his quantum mechanical perturbation treatment. The softness parameter (E^\ddagger) for some acids and bases is indicated in parentheses in Table 1.8 and 1.9. The high positive and negative E^\ddagger values indicate hard acids and bases, respectively.

It is evident from these tables that the hardness or softness of a given element varies greatly depending on the charge and the nature of surrounding groups. For example, BF₃, BMe₃, and BH₃ have been classified as hard, borderline, and soft acids, respectively. This situation is quite analogous to that which we encountered earlier in our discussion of electronegativity. Indeed, species having high electronegativities are generally hard and those having low electronegativities are generally soft. In this connection, it should be recognized that, although Li metal is electropositive, the Li⁺ ion is highly electronegative.

Unlike the Woodward-Hoffmann rule, the HSAB principle does not always predict in an unequivocal manner if a given reaction will be facile or not. It does usually permit us, however, to predict which of the two closely related reactions will be more facile. For example, it has been successfully employed in explaining the regiochemistry of a number of reactions which ambi-

dent species undergo. Thus the reaction of the enolate anion derived from acetophenone with EtI and $\text{Et}_3\text{O}^+\text{BF}_4^-$ gives the O-alkylation/C-alkylation ratio of 0.1 and 4.9, respectively (1.27)(eq. 1.11). This trend is readily explained by the HSAB principle.



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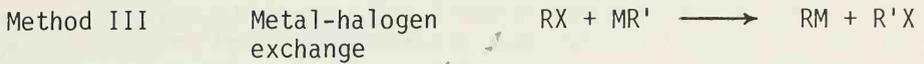
2

METHODS OF PREPARATION OF ORGANOMETALLIC COMPOUNDS

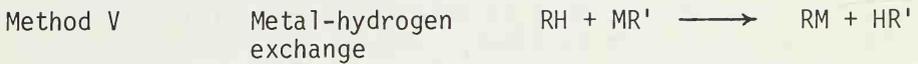
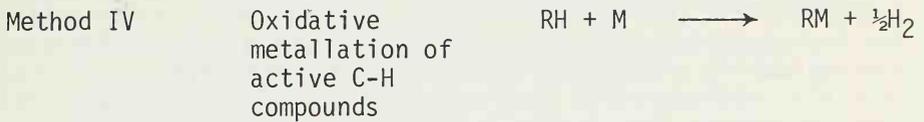
Although numerous methods for the preparation of organometallic compounds are known, the great majority of them can be classified into a dozen or so categorically different methods (Table 2.1). Organic halides, organic compounds containing active C-H bonds, and unsaturated organic molecules, such as olefins, acetylenes, and arenes, are the three most common groups of organic starting materials. In addition to these compounds, certain organometallic compounds themselves often serve as precursors to organometallic compounds containing different metals. Transformations between two organometallics containing the same metal, however, are not included in the following discussion, as these are better viewed as reactions rather than preparations of organometallics.

Table 2.1 Methods of Preparation of Organometallic Compounds

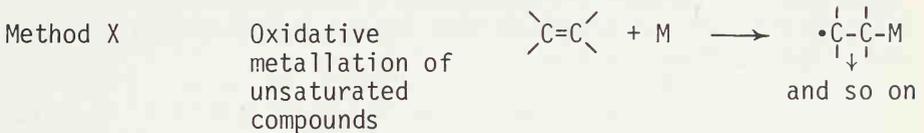
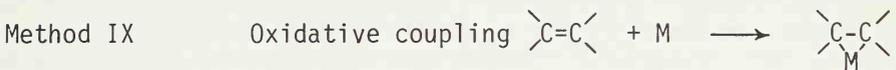
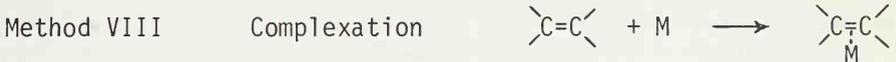
Method	Description	General equation
From halides		
Method I	Oxidative metallation of organic halides	$RX + 2M \longrightarrow RM + MX$ or $RX + M \longrightarrow RMX$
Method II	Oxidative displacement of halogen by metallate anions	$RX + ^-ML_n \longrightarrow RML_n + X^-$



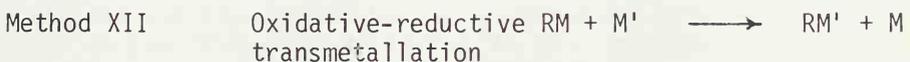
From active C-H Compounds



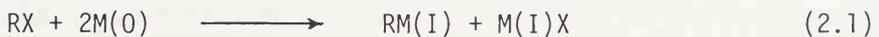
From unsaturated compounds



From organometallics



2.1 OXIDATIVE METALLATION OF ORGANIC HALIDES (METHOD I)



or



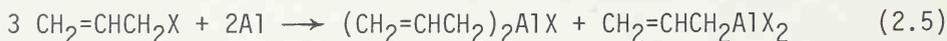
The reaction between a metal and an organic halide provides one of the most important and general methods of preparation of main group and transition metal derivatives. The method is especially suited for the preparation of organometallics of readily oxidizable or ionizable metals, that is, those of low ionization energies (IE), (Appendix IV). Among the main group metals lithium and magnesium participate in this reaction quite readily, thereby making organolithiums and Grignard reagents readily accessible. Other metals that can react readily with organic halides include Ca, Sr, and Ba. Although their reactivity appears roughly comparable to that of organolithiums, information about these organometallics is scanty. One of the often troublesome side reactions is the Wurtz coupling which involves the reaction of the product (RM) and the starting material (RX).



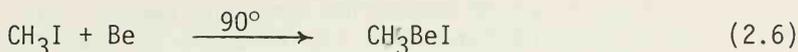
Thus the method tends to fail in cases where the product and/or the starting material are highly reactive. For this reason, organometallics of higher alkali metals, such as sodium and potassium, as well as allylic, propargylic, and benzylic organolithiums are not readily obtainable by this method. By slow addition of the halide to an excess of finely divided metal at low temperatures, however, this difficulty can be minimized. For example, the relatively stable arylsodiums are readily obtained by using fine dispersions of sodium or the liquid sodium-potassium alloy and stirring them efficiently.



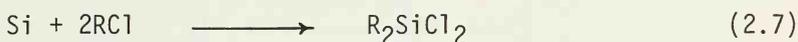
In general, the reactivity of organic halides increases in the order $\text{Cl} < \text{Br} < \text{I}$. When the metal is of relatively low reactivity, only highly reactive organic halides may be used. Thus zinc reacts satisfactorily only with (1) alkyl iodides, (2) allylic and propargylic halides, (3) α -halocarbonyl derivatives (Reformatsky reagent), and (4) other reactive halides, such as α -halo ethers. As discussed in this section, however, zinc powder obtained via reduction reacts with alkyl and aryl bromides. Aluminum and beryllium are only of limited utility in this reaction. The reaction of allyl halides with aluminum produces the corresponding sesquihalides (sesqui = 3/2 or 1.5).



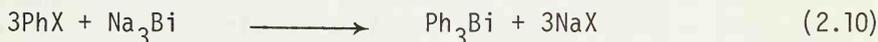
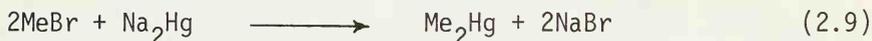
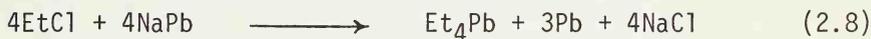
Beryllium reacts only when heated with alkyl halides.



Cadmium and boron do not appear to participate readily in this reaction. At high temperatures Si, Sn, and Sb (also phosphorous and arsenic) react with alkyl halides to form the corresponding organometallic derivatives. For example, when volatile organic halides are passed over silicon, mixed with copper and heated at 250 to 400°C, organosilicons are formed. This reaction is of commercial importance and is often called "direct synthesis."



Organometallic derivatives of Hg, Tl, Sn, Pb, Bi, and so on, can be prepared by the reaction of the alloys of these metals with alkali metals, such as sodium. These reactions must initially form the organoalkali metal compounds, which then undergo transmetallation reactions. This so-called "alloy method" is used in the manufacture of tetraethyllead, an antiknock additive in gasoline.



Certain low-valent transition metal complexes, such as those containing Ni(0) and Pd(0), undergo facile oxidative metallation (or oxidative addition) reactions with various organic halides. These reactions are discussed later in detail (Sect. 8.3).

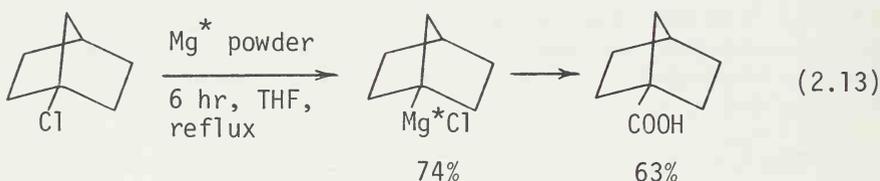
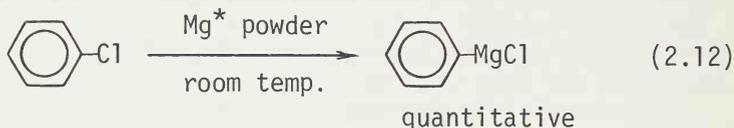
2.1.1 Metal Powders

A potentially useful method for generating highly reactive metal powders through reduction of the metal salt with an alkali metal in an etherial or hydrocarbon solvent has been developed by Rieke (2.1).

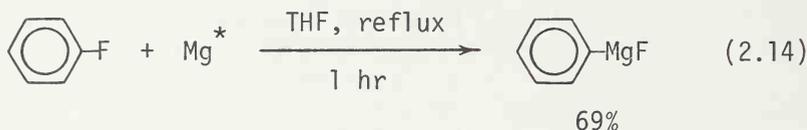


Potassium is an alkali metal often used because of its high reactivity and low melting point. Highly reactive metal powders including those of Mg, Zn, Cd, Al, In, Tl, Sn, Cr, Ni, Pd, Pt, U, Th, and Pu have been prepared by this method.

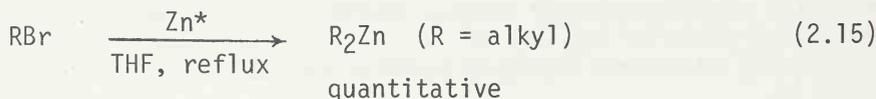
The preparation of magnesium and zinc powders using this method is of special synthetic significance in that the highly reactive magnesium and zinc powders can now be utilized in preparing those Grignard and organozinc reagents that are otherwise difficult to prepare, as exemplified by the following equations.

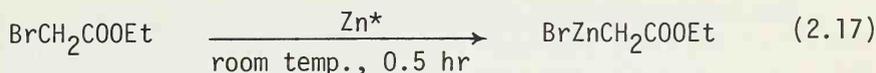


All previous efforts to prepare the Grignard reagent from fluorobenzene and magnesium had failed. On the other hand, magnesium powder generated by the reaction of MgCl_2 with potassium in the presence of KI reacted with fluorobenzene to form phenylmagnesium fluoride (2.2).



Whereas commercially available zinc does not readily react with organic bromides, Rieke's zinc powder generated from anhydrous ZnCl_2 and potassium in THF readily reacts even with alkyl and aryl bromides as shown in the following equations (2.3).





The reaction of Ni, Pd, and Pt powders is discussed later (Sect. 8.3).

2.1.2 Metal Vapors as Reagents

So far we have dealt with either polymeric metals, as in the preparation of Grignard reagents, or metal-ligand complexes, such as $\text{Ni}(\text{PPh}_3)_4$ and $\text{Pd}(\text{PPh}_3)_4$. There is, however, at least one more way to utilize metals as reagents. Metals can be vaporized as mainly monoatomic species, and such species have been widely used to plate plastics in industry. Although these metal vapors had received little attention from synthetic chemists until recently, intensive studies by Skell (2.4), Timms (2.5), Klabunde (2.6), and others have clearly established that metal vapors are highly reactive and useful reagents in the preparation of organometallics, providing routes to even those organometallics that are otherwise inaccessible.

The technology of metal vaporization is well established (2.7), and a simple metal atom reactor is now commercially available from Kontes, Vineland, N.J. In short, metals are vaporized at high temperatures using resistive or inductive heating, electron guns, lasers, or arcs in a vacuum chamber (10^{-3} to 10^{-6} torr). Metal vapors deposit on the inside walls of the reactor kept at liquid nitrogen temperature, while vapors of organic substrates are directed through a shower head, codeposited in the same area, and allowed to react with the metal vapors.

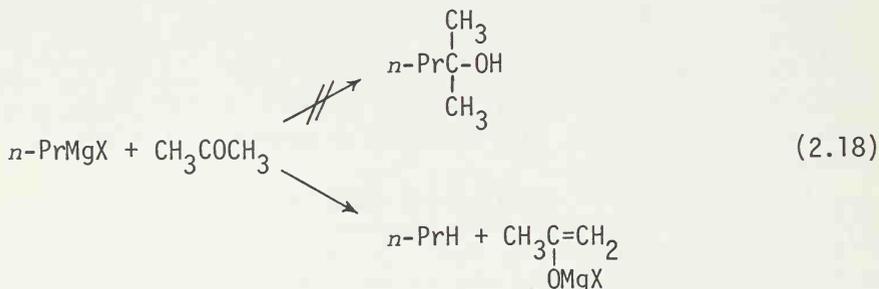
Metals that have been utilized include both main group metals, such as Li, Mg, Ca, Zn, Cd, B, Al, In, Si, Ge, and Sn, and transition metals, such as Ti, Zr, V, Nb, Ta, Cr, Mo, W, Mn, Fe, Ru, Co, Ir, Ni, Pd, Pt, Cu, Ag, Au, U, and various lanthanide metals.

Although the method is quite general, it is not without some serious difficulties and limitations. Firstly, repolymeri-

zation of the metal vapors, which usually takes place readily even at 77° K, is always a competitive low activation energy process. Therefore, the use of a large excess (>100x) of organic substrates is desirable. Secondly, since organic substrates must enter the reactor as vapors, only those substrates that boil at about -80 to 200°C at atmospheric pressure can be utilized conveniently.

The reactivity of each metal-substrate pair depends on a number of factors, such as (1) acid-base properties, (2) availability of orbitals for complexation, and (3) electronic spin state of the metal atom. It can be said that nearly all substances with π or nonbonding electrons tend to react with atomic metals to form at least weak complexes. Among organic compounds, organic halides and unsaturated hydrocarbons have been most extensively utilized. Some noteworthy reactions observed with organic halides are discussed here, and those with unsaturated hydrocarbons are discussed later.

Nonsolvated Grignard reagents can now be prepared from magnesium and organic halides (2.8). These nonsolvated Grignard reagents exhibit some unusual properties. For example, they do not undergo the usual addition reaction with acetone, the only reaction observed being proton abstraction (eq. 2.18).



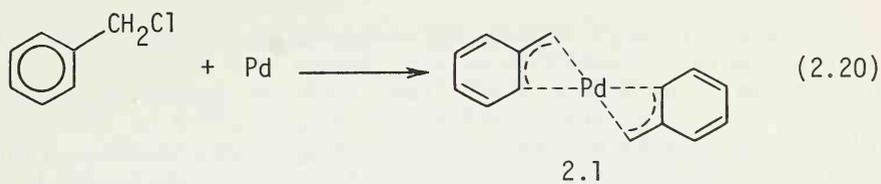
Calcium atoms react very efficiently with perfluoro olefins and hexafluorobenzene to yield C-F insertion products, see eq. 2.19 (2.9)



These appear to be the only examples of the metal insertion reaction involving the C-F bond.

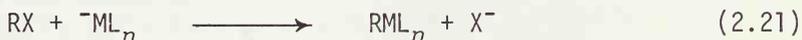
The reaction of nickel and palladium vapors with organic

halides produces oxidative addition products of the RMX type (M = nickel or palladium which are not stabilized with any ligands (2.10). These species may prove useful in examining various catalytic reactions involving these metals. As might be expected, these products (RMX), which are still coordinatively unsaturated, are generally unstable even at room temperature except for perfluorinated derivatives. The reaction of palladium atoms with benzyl chloride, however, directly produces a dimeric η^3 -benzyl-palladium derivative (2.1) which is stable up to 100 to 110°C in the solid state (2.10b).



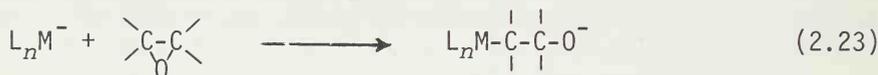
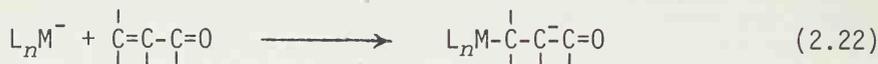
Although the scope of studies on the metal vapor-organic halide reaction is still limited, the following generalization can tentatively be made. Firstly, the general order of reactivity of organic halides is: RI > RBr > RCl. Secondly, aryl and benzyl halides react much more efficiently than alkyl halides. These results are in general agreement with those observed with either polymeric metals or metal complexes. As a preparative method to be used in practical organic synthesis, this new technique in most cases does not yet provide advantages over conventional methods. It shows high promise, however, (1) as a tool for investigating mechanistic details and (2) as a method for preparing otherwise inaccessible or less accessible species.

2.2 OXIDATIVE DISPLACEMENT BY METALLATE ANIONS (METHOD II)

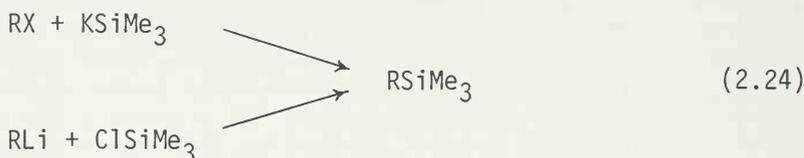


In the oxidative displacement reaction shown in eq. 2.21, the organic halide acts as an oxidizing agent, and the formal oxidation number of the metal increases by 2. The metallate anions of the IA to IIIA main group metals are essentially unknown. On the other hand, the IVA to VIA main group metals, such as Si, Sn, and Sb, as well as a number of transition metals, such as Fe, Co, Ni, and Cu, form various types of metallate anions that act as nucleophiles. In fact, some of the metallate anions containing transition metals are among the strongest nucleophiles known to chem-

ists (2.11). The metallate anions can react with a variety of electrophiles, such as organic halides, α,β -unsaturated carbonyl derivatives, and epoxides, thereby providing a convenient route to organometallics.

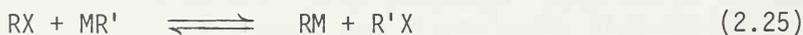


The reaction of organic halides with metallate anions containing certain transition metals, copper and iron in particular has proven to be highly significant from the viewpoint of organic synthesis. The synthetic utility of the reaction of the Group IVA to VIA metallate anions, such as $KSiMe_3$ and $LiSnBu_3$, with organic halides is not clear, because the same products can be obtained generally more conveniently from the reaction of the halogen derivatives of these metals with a variety of organometallic reagents.



Moreover, the metallate anion reaction occurs readily and selectively only with alkyl halides and sulfonates containing a $C_{sp^3}-X$ bond. In such cases, the reaction presumably proceeds by the S_N2 mechanism. Although silanions and other metallate anions react with aryl halides to produce the arylated derivatives, such reactions evidently proceed via benzyne and are therefore associated with the well-known regiochemical and stoichiometric ($R_3M^-/ArX = 2/1$) problems (2.12).

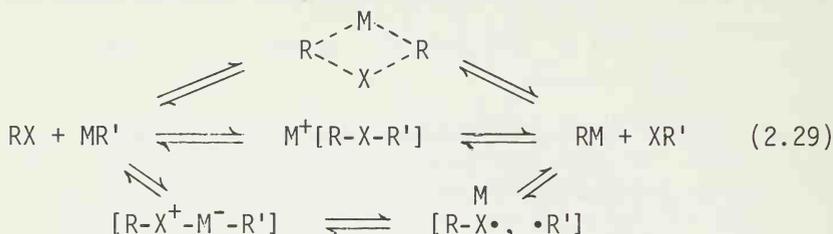
2.3 METAL-HALOGEN EXCHANGE (METHOD III)



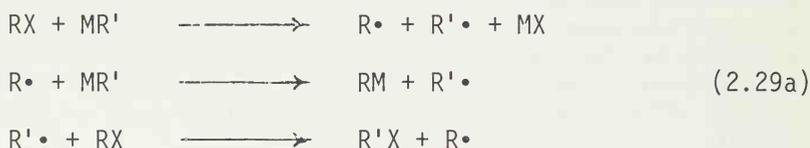
X = halogen

The reaction can proceed forward when group R is more electronegative or acidic than group R' (pK_a of RH < pK_a of R'H). It

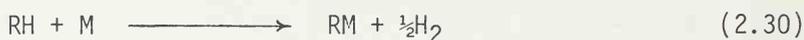
Although not well established, when stereochemically rigid organolithiums are involved, retention of configuration seems to be the rule. These stereochemical data do not tend to favor any mechanism involving alkenyl free-radicals but do not rule out one-electron processes. The following mechanisms have been suggested, but at the present time they appear to be no more than mere speculations (1.14).



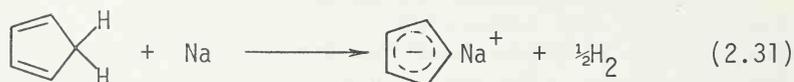
The following radical chain mechanism has been proposed for the reactions of alkyllithiums with alkyl halides (2.16).



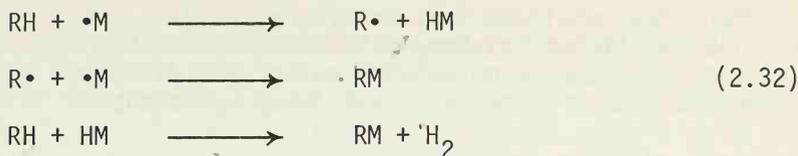
2.4 OXIDATIVE METALLATION OF ACTIVE C-H COMPOUNDS (METHOD IV)



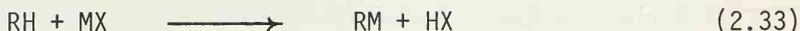
The method is far more limited than the corresponding reaction of organic halides (Method I). The reaction generally requires relatively acidic hydrocarbons ($\text{p}K_a \leq 25$ to 30), such as acetylenes and cyclopentadiene, and highly electropositive metals, such as alkali metals, as shown in the following example (eq. 2.31).



In cases where favorable results are obtained, however, the reaction provides a convenient and direct route, the only byproduct being hydrogen. Although not clear, the following dual-path mechanism may tentatively be suggested as a plausible scheme.



2.5 METAL-HYDROGEN EXCHANGE (METHOD V)



Although represented by the same general equation (eq. 2.33), there are at least two distinct processes that should be discussed here. One involves a simple acid-base reaction in which a metal-containing reagent acts as a base, whereas in the other reaction the metal containing reagent acts as a Lewis acid.

2.5.1 Metal-Hydrogen Exchange with Basic Reagents

The metal-hydrogen exchange reaction with basic metal-containing reagents provides a very general route to organometallics. The reagent itself is frequently an organometallic compound. For the reaction shown in eq. 2.33 to proceed forward, the starting compounds (RH) must be more acidic than the conjugate acid (HX) of the basic reagent. A simple thermodynamic calculation tells us that a difference of only 2 to 3 $\text{p}K_a$ units should be sufficient to drive the reaction to completion (>98%). In practice, however, a greater difference in $\text{p}K_a$ is required for satisfactory results, because the basicity of MX seldom reaches the maximum value corresponding to the $\text{p}K_a$ value of its conjugate acid (HX).

In addition to the $\text{p}K_a$ value of the conjugate acid (HX), the basicity of MX is also dependent on various other factors including the electronegativity value of the gegenion (M) and the solvent used. These factors exert marked influence on the metal-hydrogen exchange reaction.

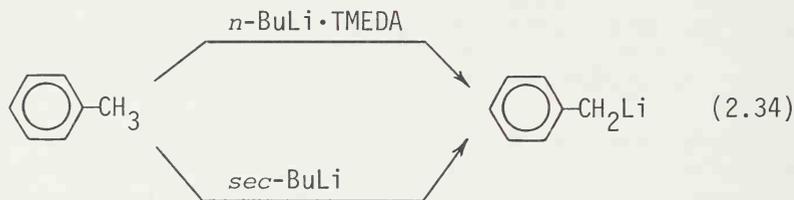
2.5.1.1 Gegenion

With a given anionic species (X), the basicity of MX decreases as the electronegativity of M increases, the approximate order being: Cs > Rb > K > Ba > Sr > Na > Ca > Li > Mg. Other less electropositive metals are of little use in this reaction. Let us consider the reaction of the *n*-butylmetals of K, Na, Li, and Mg(X) with *n*-butane ($\text{p}K_a = 50$), benzene ($\text{p}K_a = 43$), triphenylmethane ($\text{p}K_a = 30$), and acetylene ($\text{p}K_a = 25$). *n*-Butylmagnesium

bromide will metallate only acetylene, whereas *n*-butyllithium readily metallates triphenylmethane as well. Even benzene, but not *n*-butane, can be metallated using *n*-butylsodium. Finally, *n*-butylpotassium reacts with all these hydrocarbons.

2.5.1.2 Solvent

Strongly coordinating solvents, such as tetramethylethylenediamine (TMEDA), enhance the basicity of MX. For example, whereas *n*-butyllithium in nonpolar solvents does not metallate toluene, its TMEDA complex does, thereby providing one of the simplest routes to benzyllithium, even though a large excess (10x) of toluene is needed for satisfactory results (2.17). Alternatively, a stronger base, such as *sec*-BuLi can also be used for this transformation (eq. 2.34).



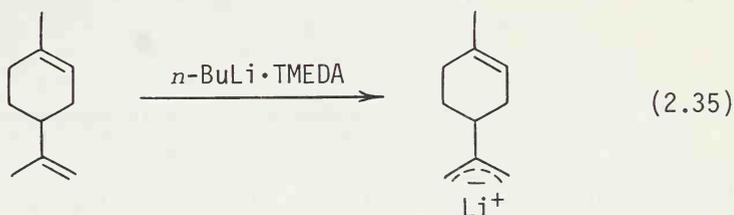
2.5.1.3 Scope

The scope of the reaction with respect to the metal was already discussed briefly. Typical saturated hydrocarbons are in most cases not acidic enough to form the corresponding organometallics by this method. As discussed later (Sect. 4.2), the metal-hydrogen exchange reaction has long been the method chosen for converting organic compounds containing relatively acidic C-H bonds ($\text{p}K_a \leq 30$) including terminal acetylenes, various carbonyl and cyano derivatives containing the α C-H bond, and cyclopentadiene derivatives. Arenes and alkenes can also be metallated readily. In cases where these compounds contain the benzylic and allylic C-H bonds, metallation can take place at both sp^2 and sp^3 carbon atoms, although the benzylic and allylic C-H bonds tend to be somewhat more reactive than the C_{sp^2} -H bonds.

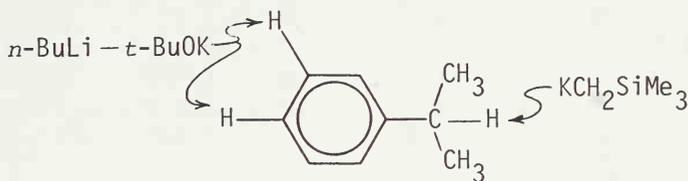
2.5.1.4 Chemoselectivity, Regioselectivity, and Stereoselectivity

Although highly versatile and useful, the metal-hydrogen exchange reaction suffers from a few serious difficulties. Since strong

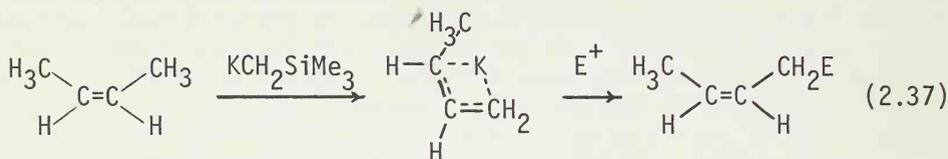
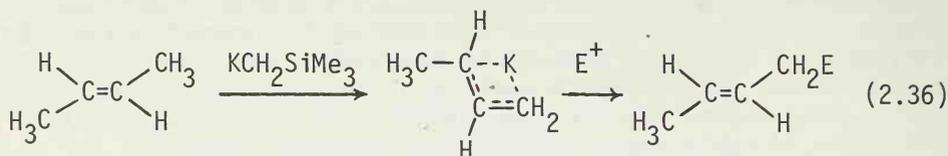
bases readily react with a variety of electrophilic functional groups, the chemoselectivity of the method is inherently low. It represents a difficult problem to overcome. Controlling the regio- and/or stereochemistry of the reaction is also problematic in many cases. Recent developments, however, permit us to exert considerable regio- and/or stereochemical control. For example, limonene can be selectively metallated at only one of the five allylic positions (2.18).



The regiochemistry of the metallation reaction is also very much dependent on the nature of the bases used. For example, whereas $\text{KCH}_2\text{SiMe}_3$ abstracts the benzylic hydrogen of cumene, a combination of $n\text{-BuLi}$ and $t\text{-BuOK}$ attacks its meta and para hydrogens (2.19).

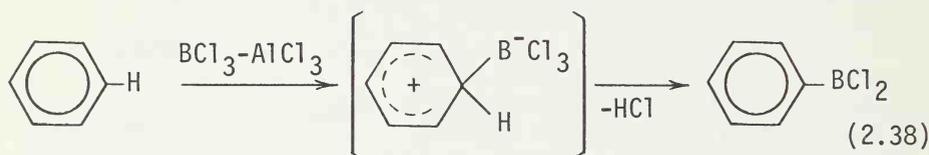


Although it still is difficult to predict accurately the point of attack in a given case, strongly basic reagents, such as $\text{KCH}_2\text{SiMe}_3$, tend to attack the most acidic hydrogen of a given molecule, whereas the reaction of weaker bases, such as $n\text{-BuLi}$ and $t\text{-BuOK}$, can be strongly influenced by other factors, such as steric hindrance. In favorable cases, the metal-hydrogen exchange reaction proceeds in a remarkably stereospecific manner, as exemplified by the following conversions; see eqs. 2.36, 2.37 (2.20).



2.5.2 Metal-Hydrogen Exchange with Acidic Reagents

Certain metal-containing reagents that are Lewis acidic, such as BCl_3 , $\text{Hg}(\text{OAc})_2$, and $\text{Tl}(\text{OCCF}_3)_3$, undergo the metal-hydrogen exchange reaction as shown in eq. 2.38. The method is most useful when RH is an arene. Many of these reactions can be best viewed as electrophilic aromatic substitution reactions involving metal-containing electrophiles, as exemplified by the following reaction (2.21, 2.22).



The reaction suffers from various difficulties and limitations associated with other electrophilic aromatic substitution reactions. Thus it often results in mixtures of regioisomers and arenes with electron-withdrawing, that is, deactivating, substituents often failing to undergo the metal-hydrogen exchange reaction. Despite these limitations, it represents one of the most direct and convenient routes to arylmercury and arylthallium derivatives (Sect. 7.2.3).

The corresponding reactions of alkenes and alkynes tend to undergo addition rather than substitution. Thus although mechanistically closely related to the aryl cases discussed above, these addition reactions are classified as the heterometallation

reaction (Method VII).

2.6 HYDROMETALLATION (METHOD VI)



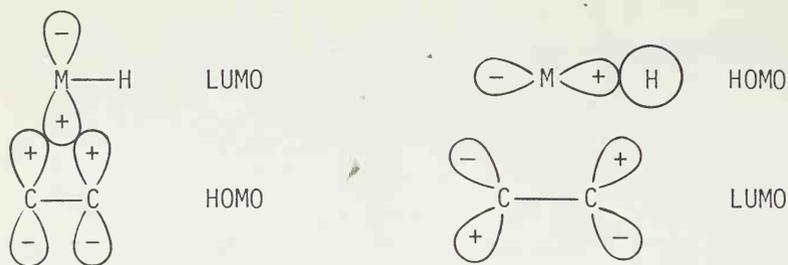
Hydrometallation is a term devised to define a reactant-product relationship. Based on the stereochemistry of the products, the known hydrometallation reactions can be classified according to the following types: (1) stereoselective cis hydrometallation, (2) stereoselective trans hydrometallation, (3) nonstereoselective hydrometallation.

2.6.1 Stereoselective Cis Hydrometallation

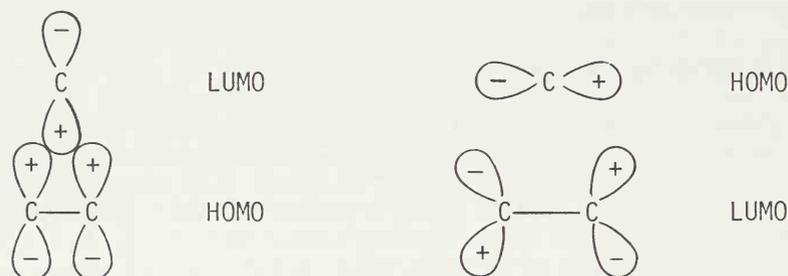
In many cases, the addition of the M-H bond to the C=C or C≡C bond is essentially 100% cis. Those metals that participate in the cis hydrometallation include a few Group IIIA and Group IVA metals, such as B, Al, and Si, and a number of transition metals. Hydroboration (Sect. 5.2.2.2), hydroalumination (Sect. 5.3.2.3), hydrosilation catalyzed by a transition metal complex, such as H_2PtCl_6 (Sect. 6.3.3.2), and hydrozirconation (Sect. 10.1), however, are the only well-developed cis hydrometallation reactions that are currently useful as methods for the preparation of hydrometallated species as discrete reagents and intermediates. Each of these reactions is discussed in detail in the sections indicated.

One of the key requirements for the cis hydrometallation reaction is that the actual reacting M-H species be coordinatively unsaturated, that is, either a 6-electron or 16-electron (possibly 14-electron) species. Although the precise mechanism of the cis hydrometallation reaction has not been fully clarified, the presently available data are consistent with the following concerted, but probably non-synchronous, mechanism which may be classified as a thermally allowed $[\pi 2_s + \sigma 2_a + \omega 0_s]$ reaction according to the Woodward-Hoffmann conservation (1.6)

Hydrometallation



Carbene Addition (singlet)

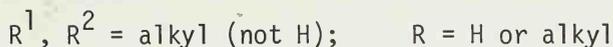
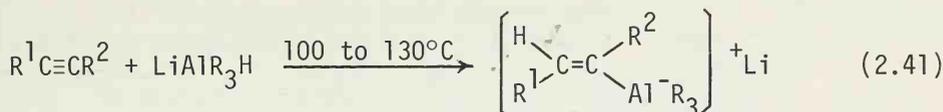


It might be instructive to compare this mechanism with that proposed for the singlet carbene reaction with olefins (2.23).

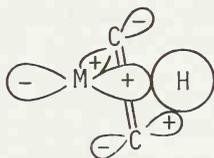
As discussed later in detail (Sect. 10.1), many other transition metal hydrides do undergo the hydrometallation reaction. In most cases, however, the hydrometallated species cannot be isolated due to various competitive side reactions, of which dehydrometallation and reduction of the hydrometallated product with the metal hydride are the most common.

2.6.2 Stereoselective Trans Hydrometallation

Although much more limited in scope, certain hydrometallation reactions involve a predominant, if not exclusive, trans addition of the M-H bond, as shown in the following example; see eq. 2.41 (2.24).



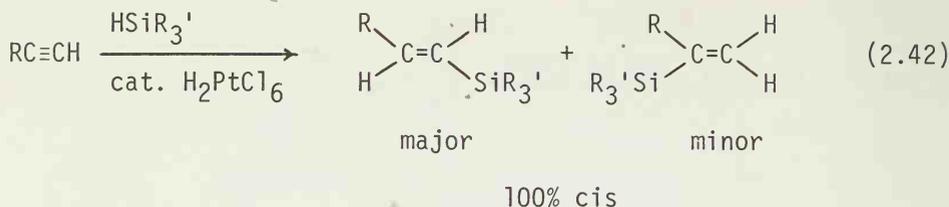
The trans hydrometallation reaction with simple olefins and acetylenes is usually a slow reaction requiring high temperatures. In some favorable cases, however, it takes place even below $0^\circ C$. Thus the reaction of hexafluorobutyne with Cp_2MH_2 ($M =$ molybdenum and tungsten) and Cp_2ReH gives the corresponding trans addition products at or below $-30^\circ C$ (2.25). The trans hydrometallation reaction of hexafluorobutyne with $HMn(CO)_5$ has also been reported (2.26). All of these metal hydrides are coordinatively saturated 18-electron species (Sect. 8.2). A concerted $[\sigma^2_s + \pi^2_a]$ mechanism has been proposed for the reaction of Cp_2MoH_2 and Cp_2WH_2 with $CF_3C\equiv CCF_3$ (2.25).



2.6.3 Nonselective Hydrometallation

Various metal hydrides including those of silicon and tin can undergo hydrometallation reactions that are not stereoselective. Some of these reactions appear to proceed at least partially by free-radical mechanisms. Hydrosilation and hydrostannation are discussed in detail in Sect. 6.3.3.

In some cases the stereochemistry of such reactions can be significantly improved by a suitable catalyst, such as H_2PtCl_6 , which can participate in (1) a stereoselective hydrometallation and (2) a transmetalation with the metal hydride used, as shown in eq. 2.42 (Sect. 6.3.3.2).



It should be clear that the applicability of such a principle is not restricted to the improvement of free-radical hydrometallation reactions. Rather, it should be applicable to the modification of any type of hydrometallation reaction.

2.7 HETEROMETALLATION (METHOD VII)

Hydrometallation, which is discussed in the preceding section, is but one of many types of addition reactions which metal-containing compounds undergo. Other bonds to metals that undergo addition reactions to the C=C and C≡C bonds include M-C, M-O, M-X, (X = halogen), and M-M bonds. Addition of the M-C bond may conveniently be termed carbometallation. Similarly oxymetallation (M-O), halometallation (M-X), and other related terms may be used to describe the corresponding addition reactions. In this book, all addition reactions of the M-X bonds other than hydrometallation and carbometallation are collectively termed heterometallation. Since carbometallation involves the transformation of one organometallic compound into another containing the same metal, it is not treated as a method for preparing organometallics.

2.7.1 Oxymetallation

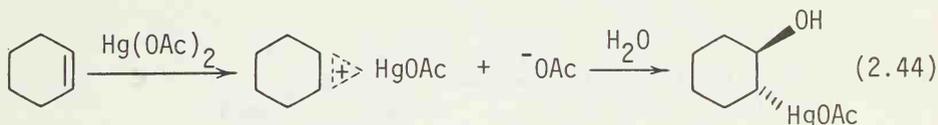
Highly electropositive metals, such as Group IA and Group IIA metals, do not generally participate in heterometallation involving the addition of the M-O (oxymetallation) and M-halogen (halometallation) bonds. This is due mainly to the fact that these metals form thermodynamically strong bonds with electronegative elements, such as oxygen and chlorine. Thus even if an addition product containing such a metal were formed according to eq. 2.43, it would readily undergo the reverse reaction, that is, β-elimination.



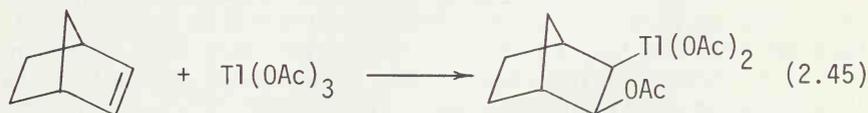
In fact, it is generally difficult by any method to prepare organometallics containing both electropositive metals and electro-negative atoms which are β to the metal as species that can be isolated.

On the other hand, certain, heavy metal compounds, such as those containing Hg, Tl, Pb, Pd, and Pt, have exhibited a strong tendency to undergo oxymetallation. One of the key requirements for oxymetallation seems to be that the metal reagent should contain a highly polarizable and hence readily ionizable M-O bond (2.27).

Both trans and cis oxymetallation reactions have been observed, although the former appears to be the more common of the two. In cases where a highly stereoselective trans oxymetallation reaction is observed, the two step mechanism involving the intermediacy of a π -complex has been proposed (2.27), as exemplified by the following.



Other nucleophilic reagents, such as water and alcohols used as solvents, have often participated in the trans oxymetallation reaction. In some cases, however, the same metal-containing reagents exhibit the opposite stereoselectivity, producing cis addition products. This cis oxymetallation has been observed with strained olefins, such as norbornene; see eq. 2.45 (2.28).



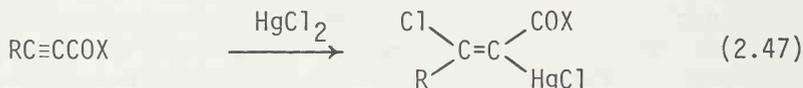
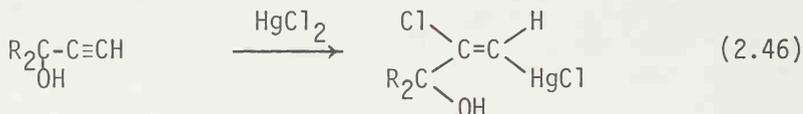
In such cases, one of the oxy ligands, rather than a solvent or an added nucleophile, is competitively incorporated into the organometallic product, somewhat irrespective of the relative nucleophilicity and concentration. It appears highly probable that the cis oxymetallation proceeds by an entirely different mechanism than that which operates in the trans oxymetallation. The

mechanistic details of oxymercuration will be discussed in Sect. 7.2.2.1. Oxymetallation involving mercury (oxymercuration) and thallium (oxythallation) represents one of the most significant routes to organometallics containing these metals and is further discussed in Sects. 7.2.2.1 and 7.4.1.3.

2.7.2 Halometallation and Other Heterometallation Reactions

Whereas oxymetallation appears unique to heavy metals, halometallation has been observed with both light metals, such as boron, and heavy metals, such as mercury and palladium. Heteropalladation is an important route to organopalladiums and is discussed in detail in Sect. 10.3.

As in the case of oxymetallation, both trans and cis halometallation reactions have been observed with heavy metals, and the trans addition appears to be the more common of the two. A few potentially useful examples of chloromercuration are shown below (2.29).



X = Me, OH, OMe, OEt, and so on

On the other hand, halometallation with haloboranes (Sect. 5.2.2.1) involves cis addition and appears to be mechanistically analogous to hydroboration. The coordinatively unsaturated nature of haloboranes, as well as the relatively high electronegativity of boron, which renders the haloborated products relatively stable to β -elimination, must be responsible for this unique cis halometallation of haloboranes.

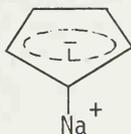
Although less common, various other heterometallation reactions, including those of the M-N (aminometallation) and M-M bonds, have also been observed. These will be discussed as we encounter them in later chapters.

2.8 COMPLEXATION (METHOD VIII)

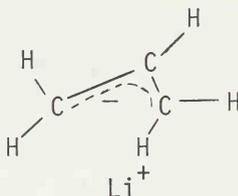
As we have already seen, coordinatively unsaturated metal-con-

taining species have a tendency to interact with electron donors to form coordinatively saturated compounds. The reaction may be viewed as a Lewis acid-Lewis base interaction, the equilibrium position of which is a function of various electronic and steric factors.

Olefins, acetylenes, and arenes are bases of low Brønsted basicity. Thus these compounds do not form stable complexes with the main group metal derivatives, although a number of π -complexes have been suggested as transient species in various reactions, such as hydroboration and oxymercuration. A number of main group metal derivatives, such as cyclopentadienyl sodium (2.2) and allyllithium (2.3), might be viewed as π -complexes of main group metals. The M-C bonds in these compounds, however, are essentially ionic rather than covalent.



2.2

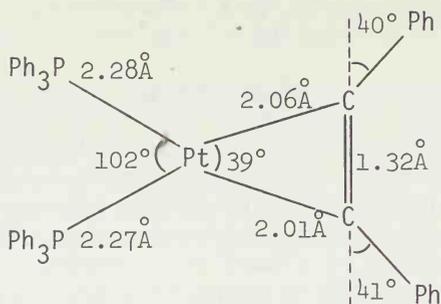


2.3

On the other hand, transition metal-containing compounds with partially filled d orbitals can act simultaneously as both a donor and an acceptor. Thus they can form highly stable π -complexes with unsaturated organic compounds. Since this π -complexation pertains only to the organotransition metal compounds, its detailed discussion is presented in Sect. 8.3.

2.9 OXIDATIVE COUPLING (METHOD IX)

Certain subvalent compounds of the main group metals (2.30), such as B-X and SiX₂, and various coordinatively unsaturated organotransition metal compounds can react with unsaturated organic compounds to form addition products, which may be viewed as σ -complexes rather than π -complexes, as exemplified by 2.4 (2.31). As might be expected, the difference between complexation and oxidative coupling can be vague. The true structure of organotransition metal compounds formed by the interaction of transition metal complexes with olefins or acetylenes may, in some cases, be best represented by a hybrid of two extreme structures representing complexation and oxidative coupling. A more detailed discussion of this subject is presented in Sect. 8.3.



This reaction is closely related to the complexation reaction discussed above, and distinction between the two is often not clear-cut. As in the case of complexation, the key requirement for the oxidative coupling reaction represented by eq. 2.48 appears to be that the metal compounds should possess both empty and filled nonbonding orbitals.



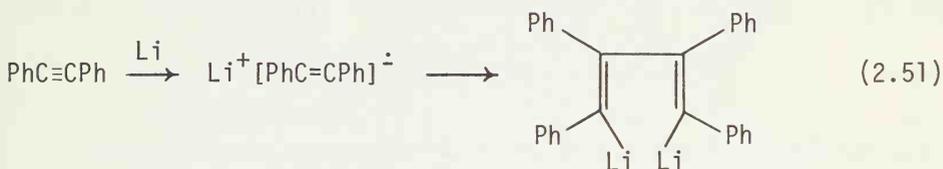
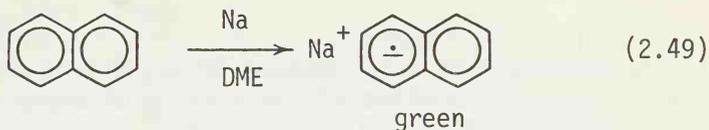
Whereas a number of transition metal compounds satisfy this requirement, relatively few main group metal compounds of this type have been known. As a result, the scope of oxidative coupling as a method for preparing organometallics of the main group metals is still quite limited. The three-membered metallocyclic products containing main group metals tend to be highly unstable, and only a small number of compounds, such as 2.5, have been prepared and characterized as such (2.32).



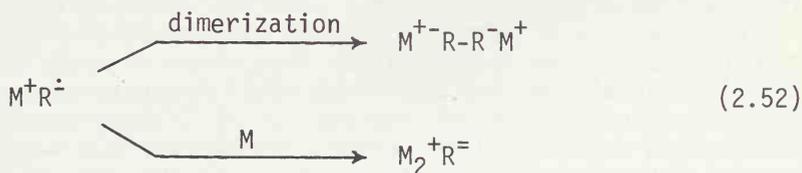
It is also instructive to point out that the oxidative coupling reaction shown in eq. 2.48 is closely related to the well-known carbene addition reaction. Oxidative coupling involving transition metals is discussed in detail in Sect. 8.3.

2.10 OXIDATIVE METALLATION OF UNSATURATED ORGANIC COMPOUNDS
 (METHOD X)

Metals of low ionization potentials can undergo one-electron transfer reactions with unsaturated organic compounds with a low-lying unoccupied orbital (LUMO) to form ion pairs consisting of metal cations and anion radicals derived from the unsaturated organic compounds. In practice, only alkali metals and conjugated olefins including arenes and acetylenes participate readily in this reaction (2.33). A few representative examples follow.

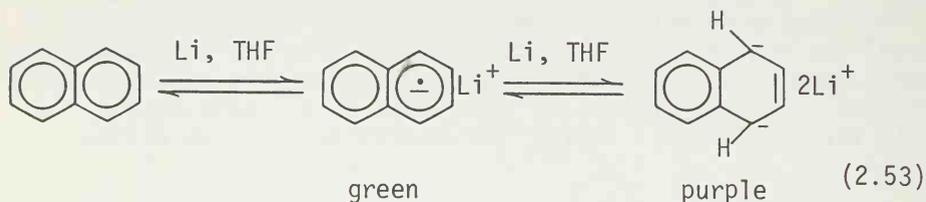


The radical anions formed by a single one-electron transfer can undergo various transformations. In the absence of any other reactive species, the radical anions tend to dimerize as shown in eqs. 2.50 and 2.51. In some cases, however, the radical anions participate in the second one-electron transfer reaction to form the corresponding dianions (eq. 2.52).

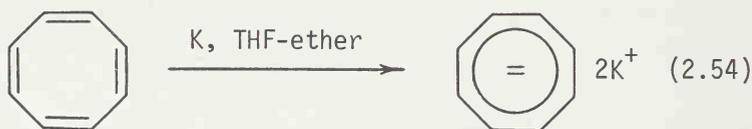


With a given substrate, formation of dianions is favored by using (1) lithium, which forms more covalent bonds to carbon than sodium and potassium, and (2) solvents of low dielectric constant

and poor solvating ability. In other words, the dianion formation is favored if the ionicity of the metal-carbon bond is low. A typical example is the formation of the dilithio derivative of naphthalene as shown in eq. 2.53 (2.34).



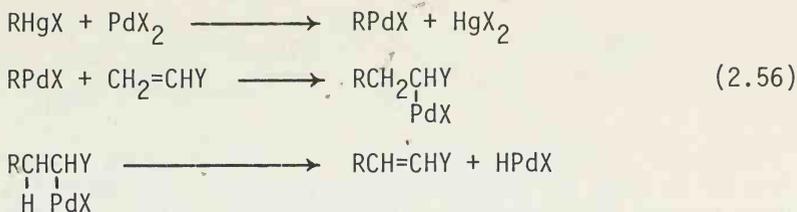
Dianion formation is also favored if the dianion is highly stabilized as in the formation of the dianion of cyclooctatetraene; see eq. 2.54 (2.35).



2.11 TRANSMETALLATION (METHOD XI)

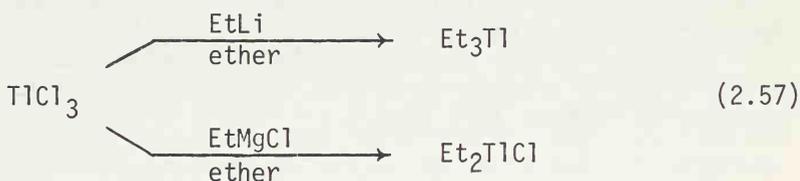


The transmetallation reaction shown in eq. 2.55, which does not involve any oxidation-reduction, is probably the most general method for preparing those organometallics that cannot be obtained directly from organic compounds. For this reaction to proceed in a forward direction, M has to be more electropositive than M'. It should be pointed out, however, that, even in cases where M is less electropositive than M', it is still feasible to generate an equilibrium quantity of RM' and utilize it in the subsequent step. Thus certain organometallics containing mercury (EN = 1.9), for example, have been successfully utilized in the vinylic hydrogen-substitution reaction shown in eq. 2.56, in which organometallics containing palladium (EN = 1.35) are products in the first step (2.36).

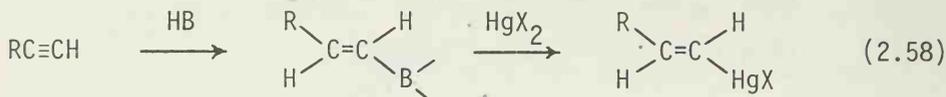


Because of their ready availability and highly electropositive nature, organolithiums and Grignard reagents have been used most extensively as parent organometallics (RM). Organometallic compounds containing essentially all metals, whose electronegativities are greater than those of lithium and magnesium, have been prepared by this method.

As might be expected from the electronegativity values, organolithiums are generally more reactive than Grignard reagents. For example, EtLi reacts with TlCl_3 to form Et_3Tl , whereas EtMgCl replaces only two of the three chlorine atoms to form Et_2TlCl .



Despite their versatility, there are a few difficulties associated with organolithiums and Grignard reagents. Firstly, as these organometallic reagents react with practically all electrophilic functional groups, it is either impossible or difficult to prepare organometallics containing some of such functional groups by this method. In such cases, the use of less electropositive metals, such as zinc and aluminum, should be considered. Secondly, it is generally cumbersome to prepare organolithiums and Grignard reagents which are stereochemically defined at the metal-bound carbon atom. On the other hand, some of such species, *trans*-alkenylmetals, for example, can be readily prepared by hydrometallation of the corresponding alkynes (Sect. 2.6). It is therefore advantageous to use these readily available substances as parent organometallics, as shown in the following synthesis of alkenylmercuries (Sect. 7.2.1).



Group X in eq. 2.55 can be an organic group. In such a case, the MX is also an organometallic product. For example, a widely used method for preparing allyllithium involves the reaction shown in eq. 2.59 (Sect. 6.4.1).



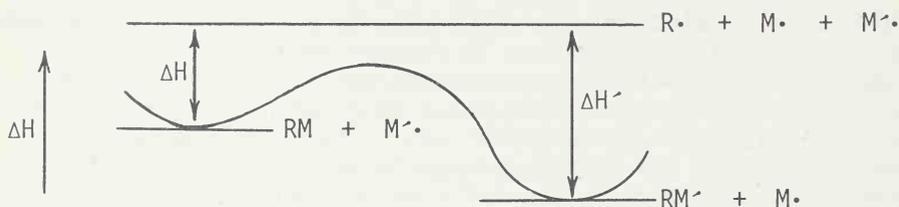
The more electronegative or less basic organic group, allyl, is nearly exclusively bonded to the more electropositive metal, lithium, in the product mixture. Thus as far as the synthesis of allyllithium is concerned, the starting allyl compound contains the less electropositive metal of the two, tin. It should be clear, however, that this fact does not contradict the general statement made above concerning eq. 2.55.

The scope of the transmetallation reaction shown in eq. 2.55 is too broad to discuss in detail, but is discussed in various sections throughout this book.

2.12 OXIDATIVE-REDUCTIVE TRANSMETALLATION (METHOD XII)



This redox reaction can proceed forward when the free energy of formation of RM is more positive (or less negative) than that of RM'.



Since few entropy data for organometallic compounds are available, the heat of formation (ΔH) rather than free energy is used here. The ΔH values for the methyl derivatives of several main group metals are summarized in Table 2.2.

Table 2.2 Heat of Formation of Me_nM^a

Me_nM	ΔH (kcal/mole)	Me_nM	ΔH (kcal/mole)
$\text{Me}_2\text{Zn}(g)$	13	$\text{Me}_3\text{Al}(g)$	-21
$\text{Me}_2\text{Cd}(g)$	26	$\text{Me}_4\text{Si}(g)$	-57
$\text{Me}_2\text{Mg}(g)$	22	$\text{Me}_4\text{Sn}(g)$	- 5
$\text{Me}_3\text{B}(g)$	-29	Me_3Bi	46

^aThese values are taken from Ref. 0.4, p. 8.

These data indicate that Me_3B and Me_4Si are stable with respect to their decomposition into the methyl and metal-free radicals (exothermic), whereas the methyl derivatives of Cd, Hg, and Bi are thermodynamically unstable (endothermic).

Since organomercuries can be directly prepared by either metal-hydrogen exchange and heterometallation (as thermodynamically unstable but kinetically stable, though toxic, compounds that can be easily handled in air at room temperature) they have been most widely used as the starting materials for this transmetallation reaction. Using organomercuries, a variety of organometallics including those that contain alkali and alkali earth metals, such as aluminum and tin, have been prepared (Sect. 7.3.1).

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3

GENERAL PATTERNS OF ORGANOMETALLIC REACTIONS

Most of the final products in organic synthesis do not contain the metal-carbon bond, although there are some biologically important organic compounds, such as vitamin B₁₂, which do contain the metal-carbon bond, and various synthetic organometallic compounds which are becoming increasingly important as final products. Thus the formation of organometallic compounds themselves seldom represents the completion of a synthesis. In the great majority of cases, they must be further transformed to produce organic compounds that do not contain the metal-carbon bond. In other words, the organometallic compounds usually act as either reagents or intermediates in organic synthesis.

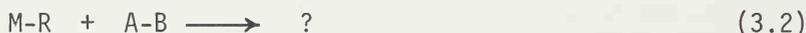
3.1 REAGENT VERSUS INTERMEDIATE

The distinction between reagents and intermediates is rather vague. One unambiguous way of defining these terms is to view any organometallic compounds a part or the whole of the metal-bound carbon group of which is to be incorporated in the organic product as intermediates and the others as reagents. It is clear that a given organometallic compound may act as an intermediate and/or reagent depending on its specific role in a given reaction. A case in point is the reaction of Grignard reagents with ketones (Sect. 4.3.2.2), which can bring about addition, enolization, and reduction as well as other miscellaneous transformations. In the addition reaction, the Grignard reagent acts as an intermediate, whereas in the reduction reaction it acts as a reagent. In a more ambiguous but perhaps more widely used definition, the reagents include, in addition to the above-defined compounds, some carbon-group-incorporating compounds that are readily accessible and relatively inexpensive so that the excessive use of such

3.2.1 Scission of the Metal-Carbon Bond

Inasmuch as carbon groups can exist and act as (1) carbanions, (2) carbocations, (3) carbon free-radicals, (4) carbenes, and (5) neutral and electron-paired species other than singlet carbenes, the organometallic compounds might, a priori, be expected to act as sources of these carbon species. It is, however, often difficult to establish unequivocally the precise mechanism of a given organometallic reaction. Fortunately, the successful use of organometallics in organic synthesis does not always require detailed mechanistic information. Even so, it may still be advantageous to attempt to interpret the observed results from the mechanistic viewpoint and to make use of the interpretations to formulate predictions.

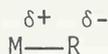
In the following discussion, let us consider only a generalized situation, represented by eq. 3.2.



The reactant A-B can represent a variety of compounds. It can be either an organic or an inorganic compound. Although not shown explicitly, groups A and B may be doubly or triply bonded. Interaction of M-R with A-B may even be preceded by decomposition of M-R and/or A-B.

3.2.1.1 Organometallics as Carbanion Sources

Probably the single most important application of organometallics to organic synthesis lies in their use as carbanion sources. By definition the metal-carbon bond is polarized in the sense indicated by 3.1. In cases where the contribution of the ionic resonance structure 3.2 is significant, the organometallic compound in question might be expected to act as a carbanion source or a nucleophile.



3.1

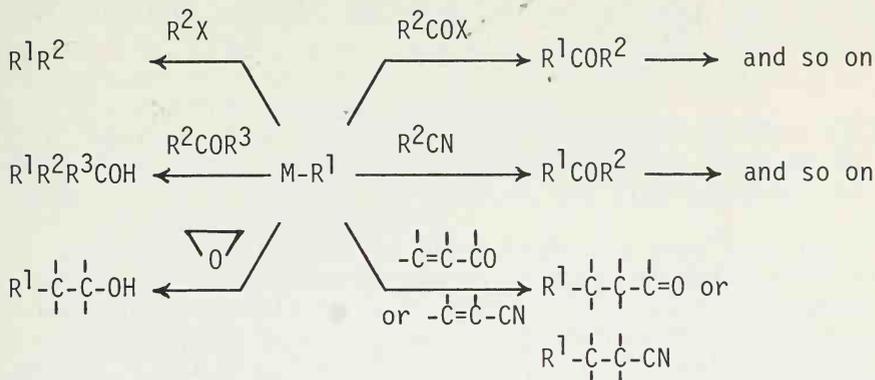


3.2

Both organic and inorganic electrophiles can react with such a nucleophilic organometallic compound. A representative scheme for the reactions of nucleophilic organometallic compounds with organic electrophiles is shown in Scheme 3.2.

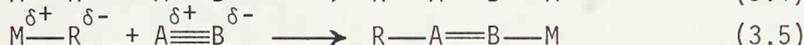
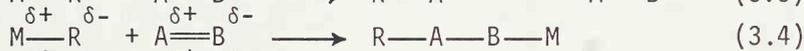
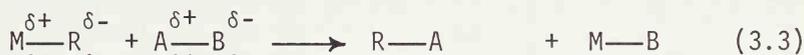
Proton acids (H-X) and halogens (X₂), along with various metal-containing compounds (M-X), represent the most commonly encountered inorganic electrophiles. Other inorganic electrophiles include those that contain the S-halogen, S-O, O-halogen, O-O,

Scheme 3.2



N-halogen, and N-O bonds. Since the reaction of a nucleophilic organometallic compound (M^1R) with a metal-containing compound (M^2X) would result in the formation of another organometallic compound either via complexation or transmetalation, it should be viewed as an organometallic interconversion reaction and is therefore discussed later.

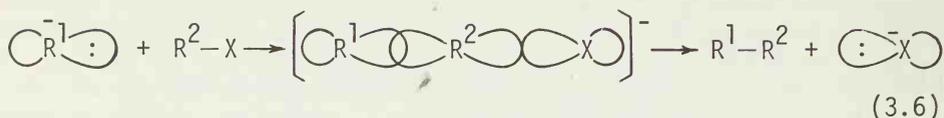
The reactant-product relationships of these reactions are straightforward and can be represented by the following general equations (eqs. 3.3 to 3.5).



On the other hand, the mechanistic details of these reactions seem to vary considerably and can be far more complex than might be indicated by these equations. A detailed discussion of the mechanisms of all of these reactions is beyond the scope of this book. Let us discuss only the case of the cross-coupling reaction between organometallics ($M-R^1$) and organic halides or sulfonates (R^2X). The following mechanistic schemes appear to be worth considering.

Bimolecular Nucleophilic Substitution Mechanism (S_N2). Until recently, there had been a tendency among chemists to associate various cross-coupling reactions of organometallic compounds with organic halides and sulfonates with the S_N2 mechanism. Among other things, the S_N2 mechanism implies a colinear arrangement of

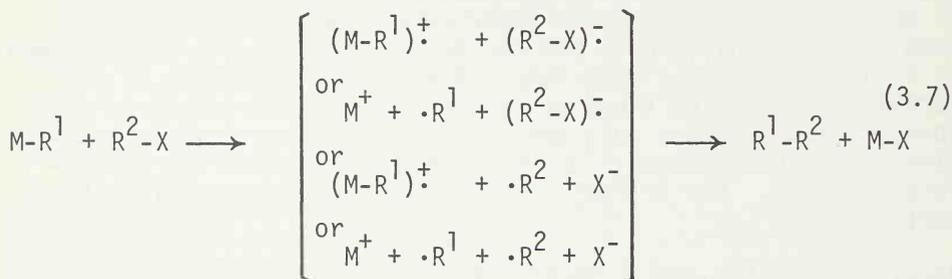
the nonbonding orbital of the carbanion and the R^2-X bond during much of the bond-forming and bond-breaking process, including the transition state (eq. 3.6).



It is clear that such a process would be favored by (1) highly electropositive metals, such as potassium and sodium, (2) highly electronegative or acidic R^1 groups, such as alkynyl groups, and (3) solvents of high coordination power, such as dimethoxyethane, which assist ionization of MR^1 through solvation of the M^+ cation.

More recent studies have indicated, however, that the S_N2 process probably represents a relatively small number of organometallic cross-coupling reactions and that it should be replaced, at least in part, with various alternate mechanistic schemes in a number of cases.

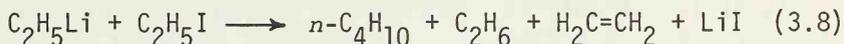
Substitution via One-Electron Transfer Process. In the S_N2 process, electron transfer and nuclear transfer take place at the same time. Alternatively, one of the nonbonding electrons of the carbanion R^1 or of the bonding electrons of M-R^1 may be transferred to R^2-X without being accompanied by any nuclear transfer. Such an electron transfer reaction will weaken not only the M-R^1 bond but also the R^2-X bond which now has one unshared electron in the LUMO. In either case, even the formation of the neutral free radicals $\cdot\text{R}^1$ and $\cdot\text{R}^2$ may occur under the reaction conditions. These radical ions and/or neutral radicals can combine to form R^1R^2 and other products (eq. 3.7).



The formation of free-radical species as transient intermediates can be detected either by ESR or by an NMR technique called "chemically induced dynamic nuclear polarization" (CIDNP), see Sect. 4.3.2.1 (3.1).

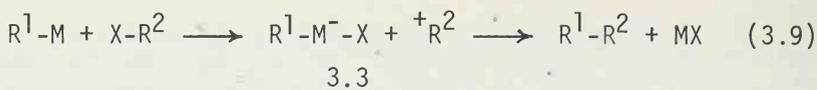
If an NMR spectrum is taken during the course of a reaction, certain signals may be enhanced, while others may be suppressed, either in a positive or negative direction. When this phenomenon, that is, CIDNP, is observed with the product of a reaction, it indicates that the product was formed either partially or entirely via a free-radical intermediate.

Many reactions of alkyllithiums with alkyl bromides, iodides, and geminal dichlorides in hydrocarbon solvents, such as the one in eq. 3.8, give products of coupling and disproportionation that show strong signal enhancements.



It should be emphasized here that the occurrence of the one-electron process is, of course, not restricted to the cross-coupling reaction, and that any two-electron process can, in principle, have its one-electron counterpart which can produce the same products. In fact, recent studies indicate that a growing number of reactions, such as addition of Grignard reagents to ketones, see Sect. 4.3.2.2 (3.2), and conjugate addition of organocuprates, see Sect. 9.4 (3.3), which were thought to proceed by two-electron processes, in many cases evidently proceed by one-electron processes (3.4).

Unimolecular Nucleophilic Substitution (S_N1) in Which the Organometallic Compound Acts as an *Amphophile*. Both the S_N2 mechanism and the one-electron transfer process discussed above involve formation of the M^+ cation prior to the crucial carbon-carbon bond formation. Consequently, such processes become less and less operative, as the metal (M) becomes increasingly electronegative. Thus, for example, typical organic derivatives of zinc (EN = 1.66) and aluminum (EN = 1.47) do not react readily with typical primary alkyl halides, such as ethyl iodide. On the other hand, these organometallics can react to form cross-coupled products with hindered alkyl halides, such as *t*-butyl chloride and isopropyl mesylate (Chaps. 4 and 5), which would merely undergo β -elimination with more ionic and basic organometallic compounds. The order of reactivity of alkyl halides, that is, tertiary > secondary > primary, clearly indicates that the reaction involves ionization or extensive charge separation of the alkyl halides and sulfonates prior to the carbon-carbon bond formation (S_N1 -like). Such a process may be induced by the interaction of the leaving group (X) and the empty orbital of the metal atom (M), where the organometallic compound acts as an electrophile rather than a nucleophile (eq. 3.9).

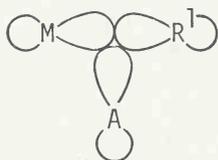


The effect of the ionization or charge separation process is synergistic in that it clearly increases not only the electrophilicity of the R^2 group but also the nucleophilicity of the $M-R^1$ bond. A subsequent nucleophile-electrophile interaction, in which the organometallic compound now acts as a nucleophile, would then produce R^1-R^2 .

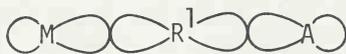
Although $M-R^1$ acts as a source of a carbanionic species (${}^-R^1$), it is not entirely appropriate to say that this organometallic reagent is acting as a nucleophile, inasmuch as its role as an electrophile is of comparable significance. We therefore propose the term *amphophile* to denote a species that can act as both an electrophile and a nucleophile in a given reaction. Of course, any dipolar molecule or group is intrinsically *amphophilic* having both electrophilic and nucleophilic ends. Therefore the use of the term *amphophile* should be restricted to those cases in which both electrophilic and nucleophilic functions are essential and of comparable significance.

Substitution via Three-Center Interaction Involving the Metal-Carbon Bond (S_E2). In the discussion of the reaction shown in eq. 3.9, nothing is said about how the R^1 and R^2 groups might interact with each other. It is conceivable that the organometallic complex 3.3 undergoes either dissociation to produce the ${}^-R^1$ carbanion which can now couple with the ${}^+R^2$ cation or the one-electron transfer. In cases where the cross-coupled products (R^1-R^2) are obtained in high yields, however, it is rather unlikely that the full-fledged carbanion is formed as an active species, since such a carbanion is expected by preference to undergo β -elimination with the ${}^+R^1$ cation.

Presently available information suggests that highly electrophilic species including carbon electrophiles may interact directly with the metal-carbon bond. Both the front-side attack (3.4) and the back-side attack (3.5) are conceivable.

3.4

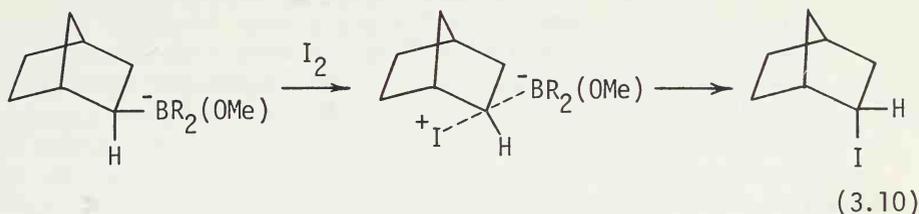
Front-side attack

3.5

Back-side attack

These processes are represented by the s_E2 mechanism (3.5, 3.6). The back-side attack mechanism should not be confused with the s_N2 mechanism. Although both are three-centered, the central carbon atom in the s_E2 process is nucleophilic, whereas that in the s_N2 process is electrophilic.

An important difference between the front-side attack and the back-side attack is that the former proceeds with retention of configuration of the R^1 group, while the latter proceeds with its inversion. A recent study of iodination of organoborates, for example, shows that the reaction proceeds with inversion. A plausible mechanism, shown in eq. 3.10, involves the back-side attack (3.7).

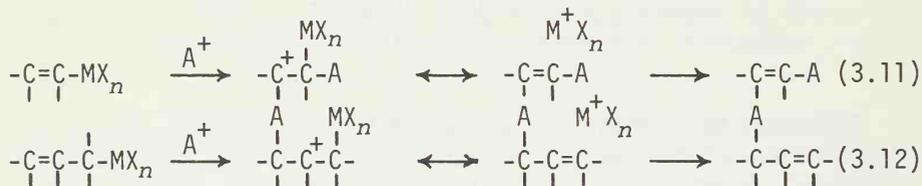


Although the number of well-established examples of the aliphatic carbon-carbon formation via organometallics that proceed by the s_E2 mechanism is still limited, it appears likely that a variety of reactions of organometallics having relatively covalent but reactive metal-carbon bonds, such as those containing Hg, Al, Sn, and certain transition metals, actually involve the s_E2 mechanisms. Although organoboranes themselves are quite reluctant to participate in these reactions, available information suggests that organoborates are sufficiently nucleophilic to react with various electrophiles. Some of these reactions appear to proceed by these mechanisms (Sect. 5.2.3).

Substitution via Addition-Elimination. Those metal-carbon bonds that are highly covalent and short, hence not readily polarizable, are generally quite resistant to the attack by electrophiles. Such metal-carbon bonds are represented by the B-C (EN of boron = 2.0) and Si-C (EN of silicon = 1.8) bonds. Thus, for example, it is exceedingly difficult to cleave the B-C bond of trimethylborane (but not of tetramethylborate) and the Si-C bond of tetramethylsilane with any electrophile including strong mineral acids and halogens, although trimethylborane is reasonably reactive toward carboxylic acids (Sect. 5.2.3.2). It may safely be concluded that these metal-carbon bonds are intrinsically nonnucleophilic.

While the generalization made above is probably true, it

does not imply that all types of B-C and Si-C bonds are reluctant to participate in reactions with electrophiles. In fact, various α,β - and β,γ -unsaturated derivatives of boron and silicon are generally far more reactive toward electrophiles than their alkyl counterparts. For example, PhSiMe_3 reacts readily with benzyl bromide to form diphenylmethane in the presence of AlCl_3 (Sect. 6.4.2.1), whereas Me_4Si is completely unreactive. What factors are responsible for such a marked difference? Firstly, the unsaturated carbon-carbon bonds, such as alkenyl, aryl, and alkynyl bonds, are reasonably good nucleophiles even in the absence of any metal. Secondly, it has now been well established that the reaction of the unsaturated carbon-carbon bonds with electrophiles is strongly facilitated by various metals, such as Hg, Pb, Tl, Sn, and Si, which are either directly bonded to or separated by one carbon atom from the unsaturated carbon-carbon bonds (eqs. 3.11 and 3.12). Such an effect has been termed σ - π conjugation effect, as discussed in Sect. 6.4.1.



It should be noted that the σ - π conjugation effect facilitates not only the interaction between the π -system and an electrophile (A^+) but also cleavage of the metal-carbon bond. This addition-elimination sequence results in the substitution of a metal atom or a metal-containing group with an electrophile.

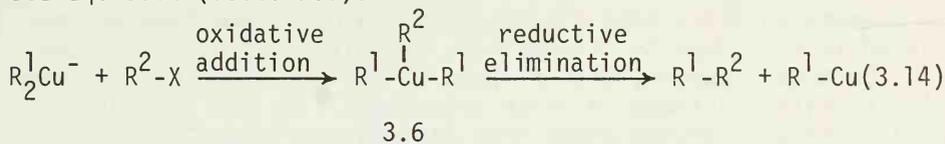
The available data indicate that similar addition-elimination mechanisms probably operate in certain reactions of α,β -unsaturated organoaluminums with electrophiles (Sect. 5.3.3.2). On the other hand, the reactions of α,β -unsaturated organoborons with electrophiles discussed in detail in Sect. 5.2.3 proceed mostly by yet another mechanism which is unique to organoborons (eq. 3.13).



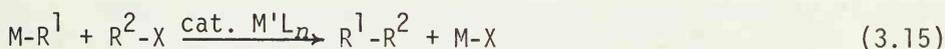
This reaction, however, does not result in the cleavage of the B-C bond, and should therefore be viewed as an organometallic interconversion reaction.

Substitution via Oxidative Addition-Reductive Elimination. Certain organotransition metal compounds can bring about cross coupling through sequences that evidently are totally different from any of the mechanisms discussed above. There appear to be at least two different paths.

The reaction of organocuprates and related compounds with organic halides has been interpreted by some chemists in terms of the following oxidative addition-reductive elimination sequence, see eq. 3.14 (Sect. 9.1).

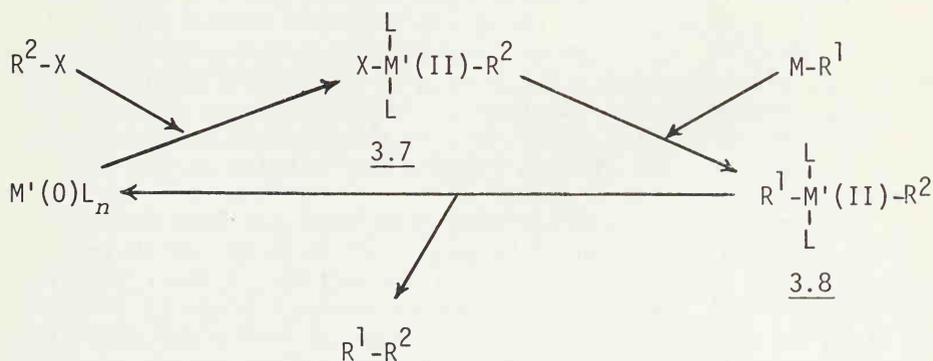


On the other hand, the reaction of certain main group organometallics ($M-R^1$) with organic halides catalyzed by nickel and palladium complexes (eq. 3.15) has been interpreted in terms of the mechanism shown in Scheme 3.3, which involves an oxidative addition-transmetallation-reductive elimination sequence (Sect. 9.2).



$M = Li, MgX, ZnX, Al,$ and so on; $M'L_n = Ni(PPh_3)_4, Pd(PPh_3)_4,$ and so on

Scheme 3.3



Although the overall equation shown in eqs. 3.14 and 3.15 clearly indicates that the R^1 group acts as a carbanionic moiety, it is not possible to classify one or the other of the two organic groups of 3.6 or 3.8 as either a nucleophile or an electrophile in the reductive elimination step which involves the crucial carbon-carbon bond formation at the expense of the cleavage of the metal-carbon bonds. These reactions are discussed in detail in Sect. 9.2.

In the above discussion, we arbitrarily chose cross coupling as a representative case of carbon-carbon bond formation via nucleophile-electrophile interaction. Similar considerations can also be made, however, with respect to various other nucleophile-electrophile reactions in which organometallics act as nucleophiles, as will become clear from various specific discussions presented in the following chapters.

3.2.1.2 Organometallics as Carbocation Sources

Since the metal-carbon bond is normally polarized as shown in 3.1, it might seem highly unlikely that any organometallic compound can act at all as a carbocation source, unless the organic group is oxidized either by added reagents or by some other means, such as electrolysis. While this generalization is valid in most cases, there are certain classes of organometallics that can readily act as carbocation sources.

One trick which organometallics can resort to in generating carbocationic species is shown in eq. 3.16.



Such a process is facilitated if both the M-X and M-R bonds are labile. It is important to recognize that the second step of the reaction involves reduction of the metal by two electrons. Consequently, cleavage of the M-R bond will occur readily if it can be easily reduced by two electrons. Indeed, various organometallic compounds containing heavy, highly polarizable metals, such as Au, Tl, Pb, Pd, and Pt, can readily participate in the reaction shown in eq. 3.16.

The carbocationic species thus generated can then undergo various reactions represented by eqs. 3.17 to 3.20, which are characteristic of any carbocations irrespective of their origins. Whereas the first two reactions produce neutral products which can exist as stable compounds, the latter two reactions yield new carbocations which must eventually undergo either hetero coupling or elimination. These reactions of the carbocations derived from organometallics of heavy metals will be discussed in Chap. 7 and Sect. 10.3.



3.2.1.3 Organometallics as Carbon Free-Radical Sources

The presence or ready availability of empty orbitals that can act as low-lying LUMOs or acceptor sites characterizes a large number of organometallic compounds. These empty orbitals can promote the formation of carbon free-radicals in a few different ways, which is briefly discussed below.

Bimolecular Homolytic Substitution (s_H2). Whereas the s_H2 reaction has almost never been observed at the carbon center, various organometallics, such as those containing boron and tin, can readily participate in the s_H2 reaction (3.8). A number of synthetically useful organoboron reactions, in particular, have been shown to proceed by the s_H2 mechanism (3.9), as discussed in detail in Sect. 5.2.3.



α -Hydrogen Abstraction. The availability of an empty orbital can facilitate the α -hydrogen abstraction reaction shown in eq. 3.22. This reaction, however, does not involve cleavage of the metal-carbon bond.



A typical example is the free-radical bromination of organoboranes discussed in Sect. 5.2.3.1 (3.10). At present, however, the scope of the α -hydrogen abstraction reactions of organometallics does not appear to have been well delineated. There are other ways of generating carbon free-radicals from organometallics which do not appear to require the availability of a low-lying empty orbital, as discussed below.

One-Electron Transfer. This process is discussed briefly in Sect. 3.2.1.1.



As mentioned earlier, this process is favored by highly electro-positive and readily ionizable metals. It is conceivable, however, that organometallate anions, such as those containing boron and aluminum, might also readily participate in this process, which would produce stable neutral species along with carbon free-radicals (eq. 3.24).

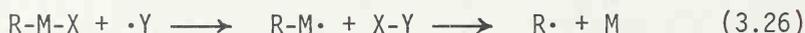


Thermal or Photochemical Excitation. Thermodynamically weak metal-carbon bonds can be cleaved thermally or photochemically (eq. 3.25).



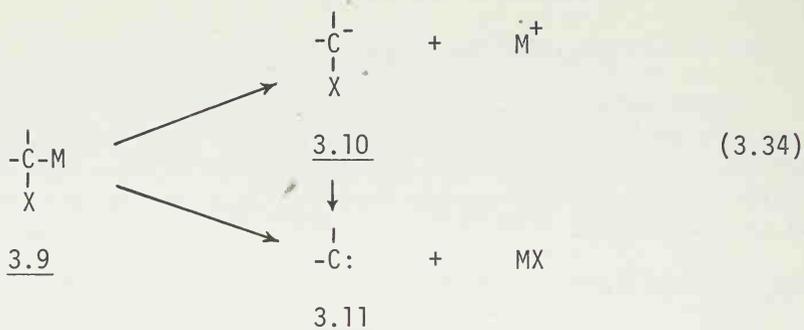
This is a reaction characteristic of any thermodynamically weak bond.

Ligand Abstraction-Reductive Cleavage. If an organometallic species contains a ligand that can be readily abstracted by a free radical, the corresponding metal free-radical may decompose to give a carbon free-radical and a reduced metal species, provided that such a reduction is facile (eq. 3.27). This is the free radical counterpart of the carbocation-forming reaction shown in eq. 3.16.



Those metals that can be readily reduced by two successive one-electron reductions, such as mercury, may participate in this re-

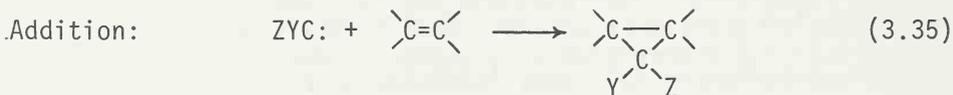
as carbene precursors and carbenoid species (3.11) (eq. 3.34).



All three carbon species in eq. 3.34, that is, 3.9, 3.10, and 3.11, are capable of acting as actual reactive species.

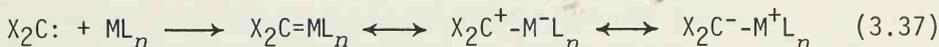
The α -haloorganometals containing highly electropositive metals, such as lithium, can be generated as unstable species which can either act as carbanions 3.10 or generate carbenes 3.11. On the other hand, α -haloorganozincs, that is, Simmons-Smith reagents, evidently react as molecular species 3.9 (Sect. 4.3.3.5). Finally, α -haloorganomercuries, such as PhHgCCl_3 , can be thermally decomposed to produce directly the corresponding carbenes 3.11 (Sect. 7.3.2.2).

The carbanion 3.10 normally acts as a typical nucleophile, unless it is converted to the corresponding carbene 3.11. The carbene 3.11 can participate in various reactions represented by eqs. 3.35 and 3.36, which are characteristic of the singlet carbenes.

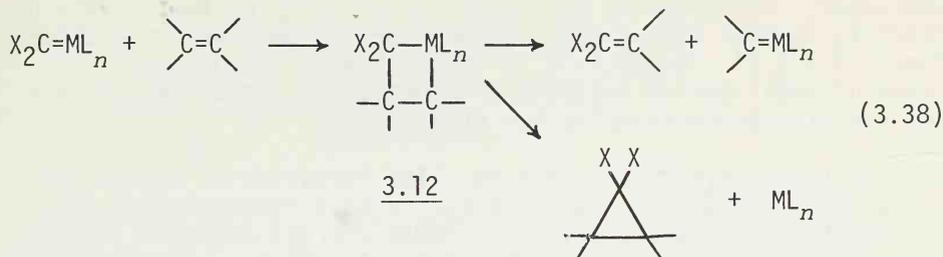


Insertion into the C-H bond does not appear to be a significant reaction of the carbenes generated by decomposition of α -haloorganometallics.

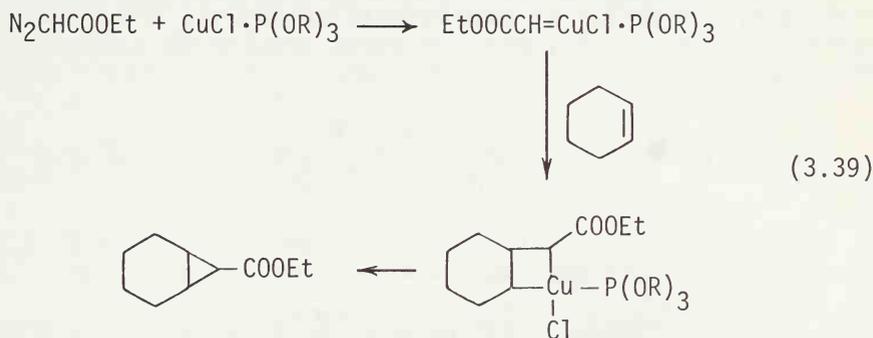
Various transition metal complexes having both empty and filled valence-shell orbitals can stabilize carbenes by forming metal-carbene complexes (eq. 3.37). As discussed in detail in Chap. 12, the metal-carbene complexes can also be formed by various other means.



One mode of metal-carbene reaction which appears to be highly general is shown in eq. 3.38.



The metallocyclic species 3.12 can undergo cycloreversion, reductive elimination, and other reactions. The formation and decomposition via cycloreversion of 3.12 appears to be one of the most plausible paths for olefin metathesis with tungsten and molybdenum catalysts (Sect. 12.3), and the formation and decomposition via reductive elimination of 3.12 can be invoked to explain the results obtained in the transition metal-catalyzed cyclopropanation (Sect. 12.1), as exemplified by the following reaction (3.12).

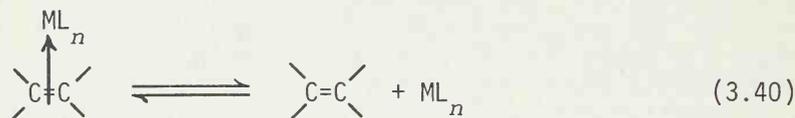


3.2.1.5 Scission of the Metal-Carbon Bond via Concerted Pericyclic Processes

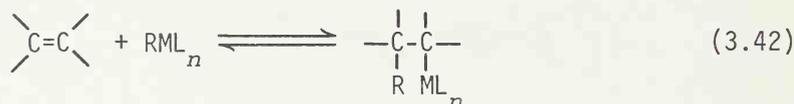
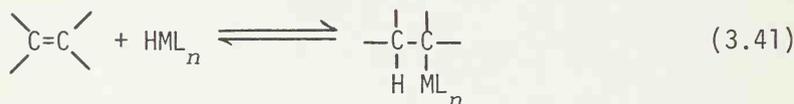
In a wide variety of reactions involving scission of the metal-carbon bond, it is difficult or almost certainly inappropriate to classify them according to one of the four general types discuss-

ed in the preceding four sections. Many of these reactions appear best interpreted in terms of pericyclic processes (1.6). It should, of course, be clear that some of the metal-carbon bond-cleaving reactions, which can be represented by the four types of processes discussed above, can also be classified as pericyclic processes. For example, the formation of :CCl_2 by thermolysis of PhHgCCl_3 is best viewed as a carbene-forming pericyclic reaction (Sect. 7.3.2.2). Because it is impossible to discuss here all types of metal-carbon bond-cleaving pericyclic reactions, only a few representative examples are presented.

Two-Electron Pericyclic Processes. The formation of various olefin π -complexes of transition metals is best represented by the two-electron pericyclic process. Their thermal decomposition by the reversal of the above process must also be two-electron pericyclic reactions.

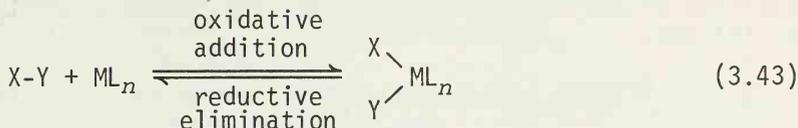


Four-Electron Pericyclic Processes. Perhaps far more intriguing are the ubiquitous thermal four-electron pericyclic processes, such as hydrometallation-dehydrometallation (eq. 3.41) and carbometallation (eq. 3.42), which at first sight might seem thermally forbidden.



In cases where the stereoselective cis addition is observed, these reactions most probably involve concerted, but not synchronous, pericyclic processes. As discussed in Sect. 2.6.1, the presence or ready availability of an empty orbital evidently makes otherwise thermally forbidden $[2 + 2]$ reactions thermally allowed. These reactions appear to be best classified as $[\pi 2_s + \sigma 2_a + \omega 0_s]$ reactions, although the mechanisms of these reactions have seldom been fully established. It also appears that

various other organometallic reactions can be interpreted in terms of the same $[\pi 2_s + \sigma 2_a + \omega 0_s]$ processes. It is likely that certain oxidative addition and reductive elimination reactions (eq. 3.43) can also be represented by this process, as discussed in Sect. 8.4.



Six-Electron Pericyclic Processes. Despite the highly covalent nature of the B-C bond, allylic organoboranes can react readily with various polar and nonpolar compounds, such as water, aldehydes, ketones, and acetylenes, as discussed in Sect. 5.2.3. Moreover all of these reactions are accompanied by allylic rearrangement. These results are best interpreted in terms of the following six-electron pericyclic mechanism.



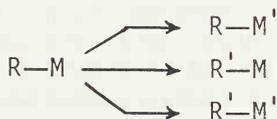
$X-Y = H-OH, RCH=O, R_2C=O, RC \equiv CR',$ and so on

3.2.2 Organometallic Interconversion Reactions

3.2.2.1 Classification of Organometallic Interconversion Reactions

Organometallic compounds can undergo reactions which convert them into new organometallic compounds. These reactions are represented by the following general scheme.

Scheme 3.4



We are now left with only the Type III reactions, which can be further divided into the following two types:

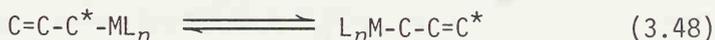
- Type A Organic ligand transformation unaccompanied by skeletal changes in the organic ligands.
1. Metal migration (metallotropy).
 2. Ligand exchange (disproportionation).
 3. Ligand displacement.
- Type B Organic ligand transformation accompanied by skeletal changes in the organic ligands.
1. Carbometallation.
 2. Ligand migration.

We briefly touch on these reactions in the following discussion.

3.2.2.2 Organic Ligand Transformation Unaccompanied by Skeletal Changes in the Organic Ligands

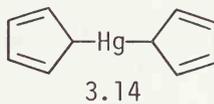
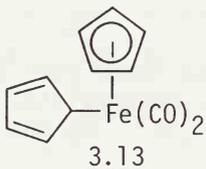
Metal Migration (Metallotropy). The $1,n$ -shift reaction of an organometallic compound produces changes in the organic ligands, although such changes in some cases are not readily discernible. The 1,2-, 1,3-, and 1,5-rearrangements appear to be the most common modes of the $1,n$ -rearrangements.

(a) Allylic rearrangement (1,3-shift). The 1,3-shift is commonly called the allylic rearrangement (3.13), and is ubiquitous in organometallic chemistry.



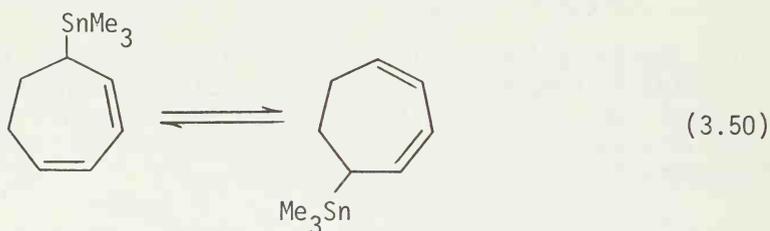
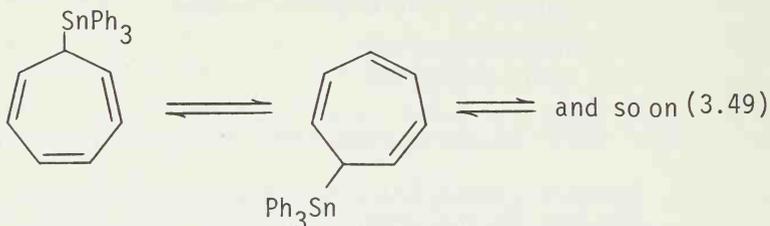
A possible explanation for the ease with which a variety of coordinatively unsaturated allylmetals undergo the 1,3-metallotropy is presented in Sect. 1.6.

(b) 1,2- and 1,5-Rearrangements. The fluxional nature of cyclic allylic organometallics, such as 3.13 and 3.14 was discovered by Wilkinson (3.14) and extensively studied by Cotton and others (3.15).

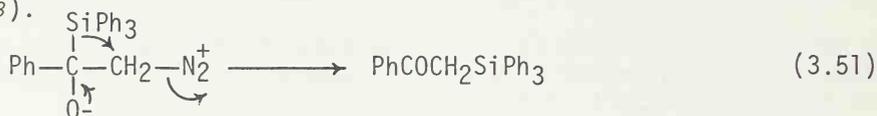


Interestingly, detailed NMR studies of the metallotropic reactions involving η^1 -cyclopentadienylmetals, such as 3.13, indicate that the 1,2- and/or 1,5-shift is favored over the 1,3-shift (3.16).

In the case of the η^1 -cyclopentadienylmetals the 1,2- and 1,5-shifts are degenerate and therefore indistinguishable. Orbital symmetry rules, however, predict that the observed processes should be represented by the thermally allowed suprafacial 1,5-shift rather than the 1,2-shift. At least in some cases, such as those shown in eqs. 3.49 and 3.50, this prediction has been borne out (3.17).



It appears that the cationotropic 1,2-metal shift is rare, although certain metal-containing groups appear to participate readily in the anionotropic 1,2-shift, as shown in eq. 3.51 (3.18).

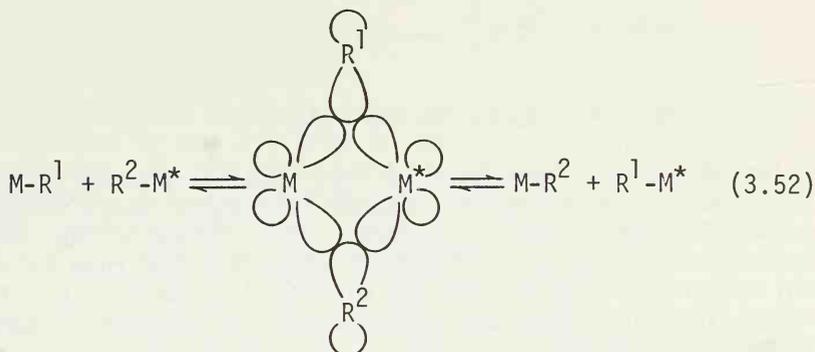


(c) Others. There are various other types of metallotropic rearrangements. For example, various ligand displacement processes discussed below, such as those involving dehydrometallation-hydrometallation and dissociation-complexation, can induce metallotropic reactions. The metallotropic reactions of organo-transition metal π -complexes are discussed in Sect. 8.5.

Ligand Exchange (Disproportionation). The ready availability of an empty valence orbital makes various organometallics labile with respect to ligand-ligand exchange (3.19). On the other hand,

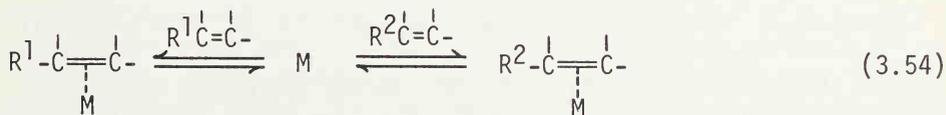
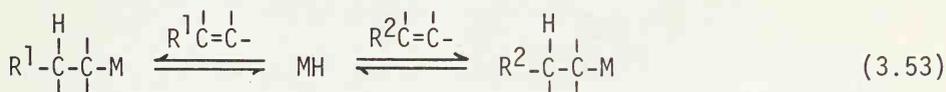
those organometallics that satisfy the Lewis octet rule, such as organosilanes, and the 18-electron rule (Sect. 8.1), are quite stable with respect to ligand exchange.

The ligand exchange process can be most conveniently studied by NMR (3.19b). It appears that the mechanism of the reaction in most cases can be represented by eq. 3.52.



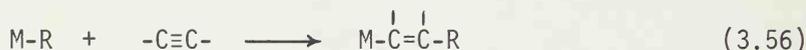
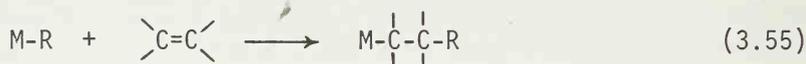
Although widely observed, this reaction does not usually seriously affect the course of organic synthesis via organometallics. It is, however, of critical importance in cases where the overall skeletal arrangement of an organometallic compound is important, as in some organoboron reactions. It is discussed later in appropriate sections.

Ligand Displacement. In the ligand-ligand exchange reaction, one ligand is displaced by another ligand. Alternatively, a ligand may be displaced by some group that initially is not bonded to a metal atom. Such reactions include (1) metal-halogen exchange (Sect. 2.3), (2) metal-hydrogen exchange (Sect. 2.5), and (3) displacement by unsaturated compounds via dehydrometallation-hydrometallation (eq. 3.53), dissociation-complexation (eq. 3.54), and other related processes.



3.2.2.3 Organic Ligand Transformation Accompanied by Skeletal Changes in the Organic Ligands

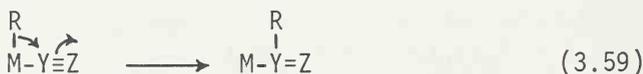
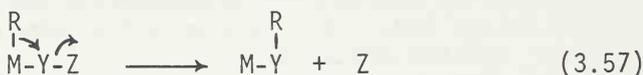
Carbometallation. This reaction may be represented by eqs. 3.55 and 3.56, and is closely related to hydrometallation (Sect. 2.6) and heterometallation (Sect. 2.7).



As in the case of hydrometallation, those carbometallation processes that proceed readily appear to require coordinatively unsaturated organometallic species. It is probable that various hydrometallations and carbometallations are governed by some common mechanism, such as the one discussed in Sect. 2.6. The carbometallation process can repeat itself to produce oligomeric and polymeric products.

In general, the carbometallation reactions of organometallics containing main group metals are much more sluggish and tend to be less important than those of certain organotransition metals discussed in detail in Sect. 10.2. Carbolithiation (Sect. 4.3.2.5) and carboalumination (Sect. 5.3.2.1), however, have found significant industrial applications.

Ligand Migration. While various types of ligand migration reactions are conceivable, by far the most common and significant is the anionotropic 1,2-shift. In this book, carbometallation is not viewed as a ligand migration reaction. The anionotropic 1,2-ligand shift of organometallics can be represented by the following general equations.

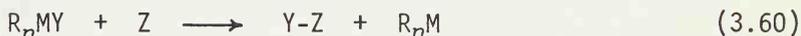


For the sake of simplicity, no formal charge signs are shown. This convention is common in organotransition metal chemistry.

At present, organoborons are the only class of organometallics of main group metals that widely participate in this reaction. Their ligand migration is discussed in detail in Sect. 5.2.3. Organotransition metal compounds, on the other hand, readily participate in various ligand migration reactions. Particularly significant, from the viewpoint of organic synthesis, is the carbonylation reaction discussed in Chap. 11.

3.3 ORGANOMETALLICS AS REAGENTS

Transfer of the carbon group from the metal via cleavage of the metal-carbon bond is the key step in the use of organometallics as intermediates. On the other hand, in the use of organometallics as reagents, transfer of hydrogen and nonmetallic heteroatom groups, such as those containing N, O, P, S, and halogens, takes place via cleavage of the respective bond to metals (eq. 3.60).



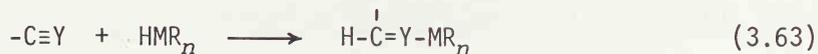
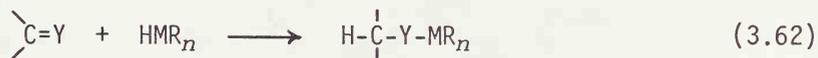
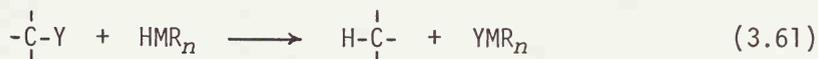
Y = H, halogen, N, O, P, and S groups, and so on

Z = organic and inorganic compounds

In some fortuitous circumstances, however, cleavage of the metal-carbon bond may also be involved.

3.3.1 Reduction via Hydride Transfer

Transfer of a hydride from a metal hydride to an organic compound brings about reduction, as represented by the following general equations.

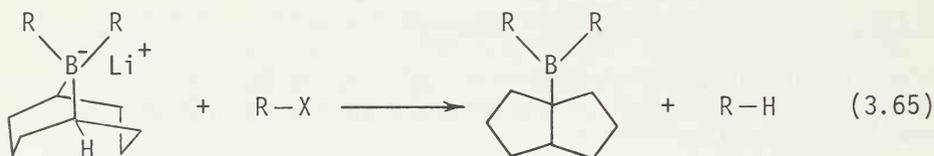
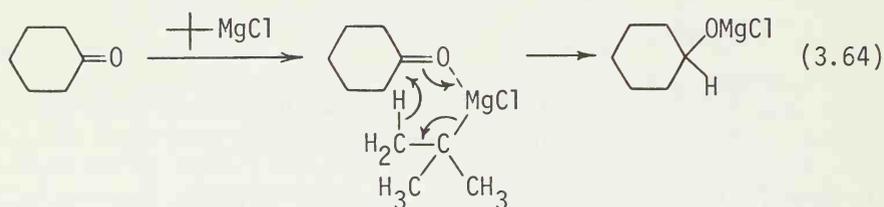


In cases where the Y group is a carbon group in eqs. 3.62 and 3.63, these equations, of course, represent hydrometallation. In other cases, the Y group is more electronegative than the carbon group, that is, $\text{C}^{\delta+}-\text{Y}^{\delta-}$. The regiochemical outcome shown in these equations stems primarily from two facts: (1) In most

cases the metal atom is more electropositive than hydrogen, that is, $M^{\delta+}-H^{\delta-}$. (2) A combination of the C-H and M-Y bonds generally is thermodynamically more favorable than a combination of the H-Y and M-C bonds, when $Y = N, O, \text{halogen, and so on}$.

Some of the most widely used metal hydrides bearing organic ligands are those that contain boron (Sect. 5.2.3.6), aluminum (Sect. 5.3.3.3), and tin (Sect. 6.4.3.3). Although various transition metal hydrides are formed as reactive intermediates, it is often difficult to prepare them as discrete reagents that can be isolated. Despite their instability, however, many of them, such as those containing the Group VIII metals and copper, hold considerable promise as selective reducing agents (Chaps. 9 and 10).

In some cases, a hydrogen atom in an organic ligand can act as a hydride. It is usually one of the β -hydrogens, as shown in eq. 3.64. Certain α -hydrogens, however, can also act as hydrides, as shown in eq. 3.65 (Sect. 5.2.3.6).



3.3.2 Organometallics as Protecting Agents

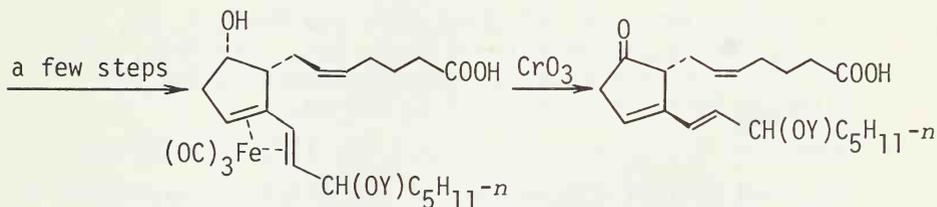
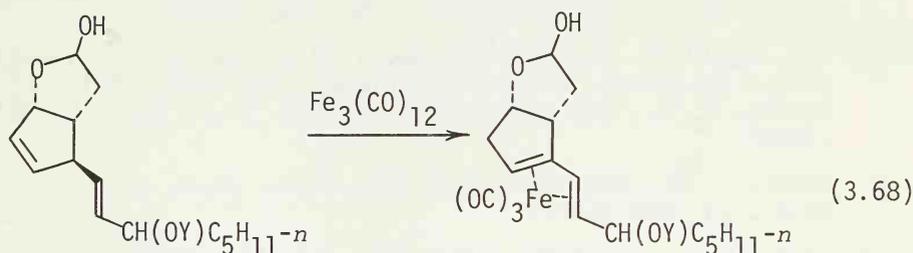
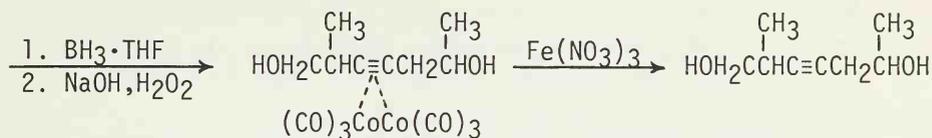
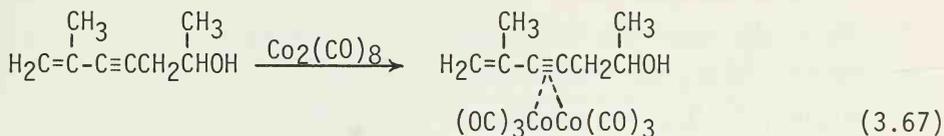
Various active hydrogen-containing functional groups can be protected by forming the corresponding organometallics.



$Y = \text{NR}_2, \text{OR}, \text{SR}, \text{and so on}$

As might be expected, those organometallics that contain relatively covalent and stable metal-carbon bonds are suited for this purpose. At present, triorganosilanes are by far the most useful class of organometallic protecting agents (Sect. 6.4.2.4).

Another significant mode of functional group protection involves formation-decomposition of organotransition metal π -complexes, as shown in the following examples; see eqs. 3.67 to 3.68 (3.20, 3.21).



(Y = THP)

There can be various other ways of protecting functional groups by means of organometallics. The subject matter, however, does not lend itself to systematic discussion. We therefore do not attempt an extensive discussion of this subject.

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PART II

**ORGANOMETALLICS OF
MAIN GROUP METALS
IN ORGANIC SYNTHESIS**

4

ORGANOMETALLICS CONTAINING GROUP IA, GROUP IIA, AND GROUP IIB ELEMENTS (Li, Na, K, Mg, Zn, Cd)

4.1 GENERAL CONSIDERATIONS

Organometallics containing Group IA and Group IIA metals are characterized by the presence of highly polar metal-carbon bonds. The Allred-Rochow electronegativity values (Appendix II) for these elements are as follows: Li(0.97), Na(1.01), K(1.04), Rb(0.89), Cs(0.86), Be(1.47), Mg(1.23), Ca(1.04), Sr(0.99), Ba(0.97), and Ra(0.97). The high polarity of the metal-carbon bonds of the organoalkali and organoalkaline earth metals is primarily responsible for both their high reactivity toward carbonyl and related polar carbon functional groups, that is, high nucleophilicity, as well as their high basicity. The terms *basicity* and *nucleophilicity* are very loosely defined in synthetic organic chemistry. The former generally refers to proton affinity, or Brønsted basicity, whereas the latter refers to the affinity toward other electrophilic centers, or Lewis basicity.

The application of francium and radium to organic synthesis is severely restricted due to their radioactivity and limited supply. Although it has become increasingly clear that organometallics containing rubidium and cesium can exhibit unique synthetic capabilities, their application to organic synthesis is still very limited. Nearly the same is true with the Group IIA metals other than magnesium. Whereas Cu, Ag, and Au can exist as d^9 and d^8 species and hence are regarded as transition metals, the Group IIB metals, that is, Zn, Cd, and Hg, do not exist in oxidation states higher than +2, and cannot therefore have incompletely filled d shells. Mercury is a heavy element of relatively high electronegativity, the chemistry of which has little resemblance to that of the Group IA and Group IIA metals. Its chemistry as well as that of thallium and lead is discussed in Chap. 7.

Because of the long history and wide-spread applications of the chemistry of organoalkali metals and Grignard reagents, it is impossible to present a comprehensive coverage of the subject. For more detailed discussions, the reader is referred to textbooks and monographs on polar organometallics (0.6, 1.14), organolithiums (4.1), Grignard reagents (0.8, 4.2), and organozincs and organocadmiums (0.8). Our discussion in this chapter is highly selective, emphasizing the chemistry of organolithiums and organomagnesiums.

4.1.1 Structure

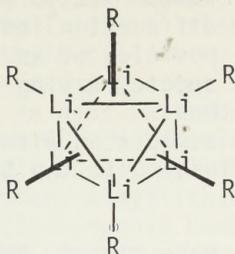
Although organoalkali and organoalkaline earth metals represent the most ionic groups of organometallics, the metal-carbon bonds of these compounds generally have appreciable covalent character. The monomeric covalent structures of these organometallics, that is, M-R and R-M-X, are coordinatively unsaturated and do not generally represent their actual structures. As discussed briefly in Sect. 1.4, organoalkali and organoalkaline earth metals usually exist as oligomeric or polymeric species, in which the monomeric units are held together via multicenter bonding.

4.1.1.1 Organolithiums

There are a few authoritative reviews on the structure of organolithiums by T. L. Brown (4.3). We have already learned that methyllithium is tetrameric in the crystalline state (Sect. 1.4). In nonpolar solvents, such as cyclohexane and benzene, sterically unhindered alkylolithiums, such as *n*-butyl- and *n*-octyllithiums, are usually hexameric, whereas sterically hindered members, such as isopropyl- and *t*-butyllithiums, are tetrameric. Benzyllithium in benzene is dimeric (4.3). In both tetrameric (1.3) and hexameric (4.1) structures, each lithium atom is bonded to three alkyl groups, and each alkyl group to three lithium atoms, via four-center two-electron bonding. In a formal sense, the lithium atom is a sextet in these compounds. No ^6Li - ^7Li coupling in ^7Li NMR has been observed, indicating that there is no Li-Li bond (4.4).

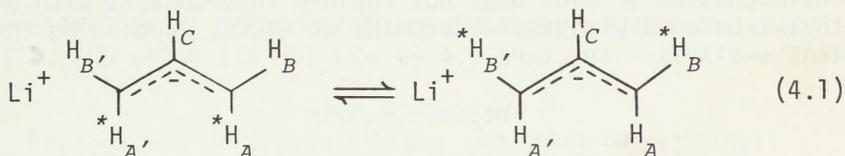
Organolithiums can form complexes with donor solvents, such as Et_2O , THF, TMEDA, and 1,4-diazabicyclo[2.2.2]octane (DABCO). These complexes are also often oligomeric. For example, the 1:1 complex between methyllithium and Et_2O is tetrameric.

Organolithiums derived from relatively acidic carbon acids, such as allyl-, benzyl-, and cyclopentadienyllithiums, have appreciable ionic character. For example, ^1H NMR spectrum of allyllithium in Et_2O or THF at low temperatures shows an AA'BB'C

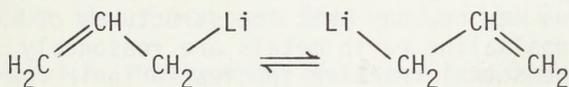


4.1

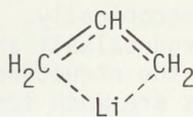
pattern in accordance with the equilibrium shown in eq. 4.1 (4.5).



At higher temperatures, a rapidly interconverting AB_4 pattern is observed. Covalent structures, such as 4.2 and 4.3, must be less important.



4.2



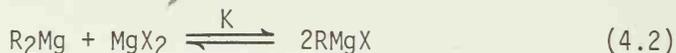
4.3

4.1.1.2 Organomagnesiums (4.6)

Typical Grignard reagents and diorganomagnesiums are monomeric in THF, which exist as THF complexes. Similar complexes can form in

ether. The structures of $\text{PhMgBr} \cdot \text{Et}_2\text{O}$ (4.7) and $\text{EtMgBr} \cdot \text{Et}_2\text{O}$ (4.8) determined by X-ray diffraction indicate that the magnesium atom occupies the central position of an essentially tetrahedral configuration. Polymeric species having a $(-\text{Mg}-\text{X}-)_n$ polymer chain can also exist in ether.

Another complication associated with Grignard reagents is their disproportionation leading to the Schlenk equilibrium (eq. 4.2).



The Schlenk equilibrium constant (K) is much larger in ether (10^2 to 10^3) than in THF (1.10). It is reasonably clear that the solvation of MgX_2 , the most Lewis acidic component of the three, governs the equilibrium and that it is more effective in THF than in ether.

^1H NMR examination of allylmagnesium bromide indicates that the α - and γ -protons are equivalent. On the other hand, isoprenylmagnesium bromide does not rapidly interconvert with 3-methyl-1-buten-3-ylmagnesium bromide at -40°C , supporting the covalent σ -allylic structure 4.4 (4.9).



4.4

In summary, although a wide variety of structures occur in the chemistry of organoalkali and organoalkaline earth metals, the common driving force for the formation of associated and/or solvated species undoubtedly is stabilization of coordinatively highly unsaturated monomeric units, that is, RM and RMX , through multicenter bonding or solvation. From the viewpoint of organic synthesis, it is important to realize that the actual reactive species are not necessarily the same as those which are observed spectroscopically. While we may now say that the structures of many organoalkali and organoalkaline earth metals are reasonably clear, the structures of the actual reactive species in their reactions are much less clear. Fortunately, this does not significantly hamper their applications to organic synthesis. For these reasons, in our subsequent discussions we adopt the conventional monomeric representations, RM and RMX , for these organometallics.

4.1.2 Configurational Stability

Since carbanions are isoelectronic with amines, free carbanions might be expected to undergo rapid inversion at room temperature.

On the other hand, covalent organometallic species are expected to exist as configurationally stable species. The configurational stability of 3,3-dimethylbutyllithium was studied by ^1H NMR (4.10). In ether, the α - and β -protons show an AA'BB' pattern at -18°C , which collapse to an A₂B₂ pattern at 30°C . The activation energy was estimated to be 62 ± 8 kJ/mole. Secondary and tertiary alkylolithiums as well as alkenyllithiums are configurationally more stable than primary alkylolithiums. Many stereo-defined organolithiums of these classes have been prepared and converted into stereochemically pure organic products. These results indicate that free carbanions may not contribute significantly to the constitution of simple organolithiums. Consideration of the relative electronegativities of various alkali and alkaline earth metals suggests that organomagnesiums should be configurationally more stable than organolithiums. By the same token, organosodiums and organopotassiums should be less stable than organolithiums. For further discussions of this subject, the reader is referred to Cram (1.12) and Bunce (1.16).

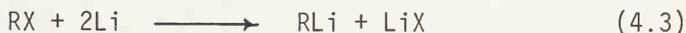
4.2 PREPARATION OF ORGANOMETALLICS CONTAINING GROUP IA, GROUP IIA, AND GROUP IIB METALS

4.2.1 Preparation of Organolithiums and Other Organoalkali Metals

Of the twelve general methods for preparing organometallics discussed in Chap. 2, oxidative metallation of organic halides (Method I), metal-halogen exchange (Method III), metal-hydrogen exchange (Method V), and transmetallation (Method XI) are of practical significance as methods for the preparation of organoalkali metals. Oxidative metallation of active C-H compounds (Method IV), oxidative metallation of unsaturated compounds (Method X), and oxidative-reductive transmetallation (Method XII) have also found some limited applications.

4.2.1.1 Preparation of Organolithiums

Oxidative Metallation of Organic Halides. The discovery that organolithiums can be prepared by the oxidative metallation of organic halides made in the early 1930s by Ziegler (4.11), Wittig (4.12), and Gilman (4.13) has made organolithiums readily available.



A large quantity of *n*-butyllithium, which is used primarily as an initiator in the polymerization of dienes, is produced by this method.

The scope of this method is broad, as indicated in Table 4.1. It is, however, less general than the corresponding method for the preparation of Grignard reagents in that those organic halides that readily undergo Wurtz coupling, such as allyl, propargyl, and benzyl halides, cannot successfully be converted into the corresponding organolithiums. Hydrocarbons, such as hexane and benzene, are preferred solvents. On the other hand, ether and THF may readily be cleaved by many organolithiums. Methyl-lithium and phenyllithium are insoluble in hydrocarbons, and their preparation usually requires the use of ethers. Fortunately, they are quite stable in ether. Alkenyllithiums are also relatively stable in ethers. Vinyl-lithium itself is commercially prepared in THF. Organic chlorides and bromides are preferred starting materials, whereas organic iodides tend to undergo Wurtz coupling extensively. Organic fluorides have almost never been used.

Various alkenyl halides have been converted to alkenyllithiums with retention of configuration. On the other hand, treatment of 4-*t*-butylcyclohexyl chloride with lithium produces a mixture of two epimers, which are themselves configurationally stable under the reaction conditions. Thus epimerization must occur during the formation of the organolithium compounds, suggesting that, at least in such a case, a one-electron transfer process appears to be operating.

Metal-Halogen Exchange. This method has been successfully used for the preparation of alkenyl- and aryllithiums (2.13). Alkyl halides are, in general, not reactive enough, while allyl, propargyl, and benzyl halides are prone to undergo Wurtz coupling. Its scope, stereochemistry, and possible mechanisms are discussed in Sect. 2.3. A few noteworthy recent developments should be briefly mentioned here, however.

Treatment of alkenyl iodides or bromides with either one equivalent of *n*-butyllithium or two equivalents of *t*-butyllithium (2.15) at low temperatures (<-50°C) produces the corresponding alkenyllithiums with retention of configuration. The second mole of *t*-butyllithium reacts with *t*-butyl halide to form isobutylene (eq. 4.4).

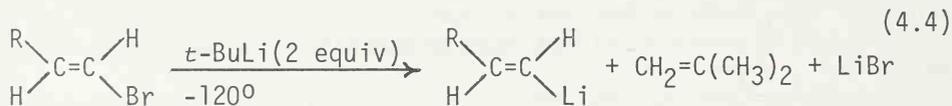


Table 4.1 Preparation of OrganoLithium Compounds

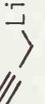
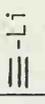
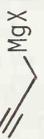
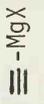
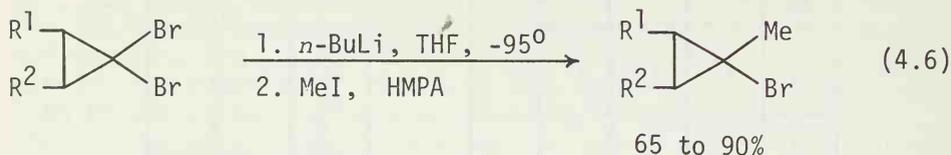
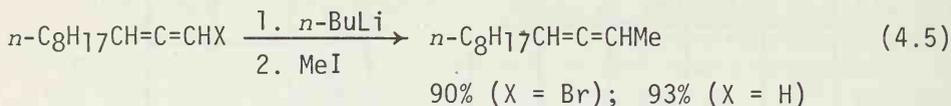
Method			PhCH ₂ Li	1°-RLi	2°-RLi	3°-RLi		ArLi	
I. RX + M	-	-	-	+	+	+	+	+	
II. RX + MR'	-	-	-	-	-	-	+	+	
V. RH + MR'	+	+	+		-	-	-	-	+
XI. RM + M'X	+		+				+		

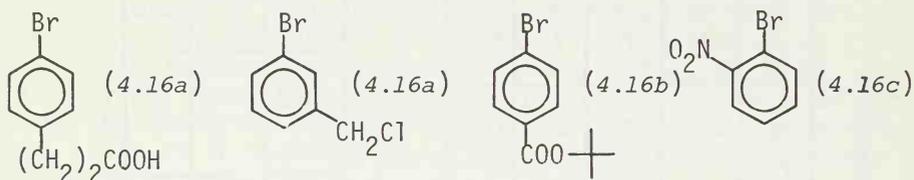
Table 4.2 Preparation of Grignard Reagents

Method			PhCH ₂ MgX	1°-RMgX	2°-RMgX	3°-RMgX		ArMgX	
I. RX + M	+	+	+	+	+	+	+	+	
V. RH + MR'									+

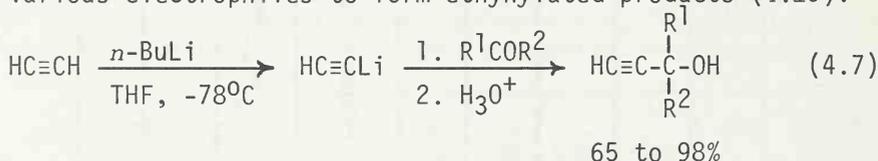
Allenyl (4.4) and cyclopropyl halides (4.15) undergo similar transformations.



It has recently been demonstrated that, at very low temperatures ($<100^\circ\text{C}$), the metal-halogen exchange reaction can tolerate various electrophilic functional groups. Some aryl halides that have been successfully converted into aryllithiums are shown below.

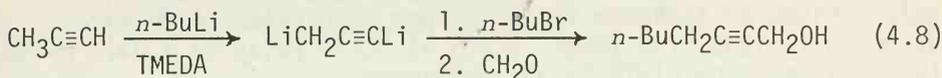


Metal-Hydrogen Exchange. The scope and limitations of this reaction as a method for preparing organolithiums are briefly discussed in Sect. 2.5.1 and summarized in Table 4.1. There are a number of extensive reviews on this subject, such as those by Wakefield (4.1) and Gilman (4.17). Consequently, a few recent noteworthy developments are briefly discussed here. At -78°C , acetylene can be converted to monolithioacetylene which can react with various electrophiles to form ethynylated products (4.18).

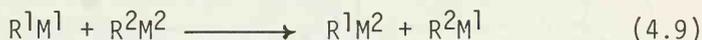


Propyne can be lithiated in both the 1 and 3 positions. The dilithio derivative can act first as a propargyllithium derivative

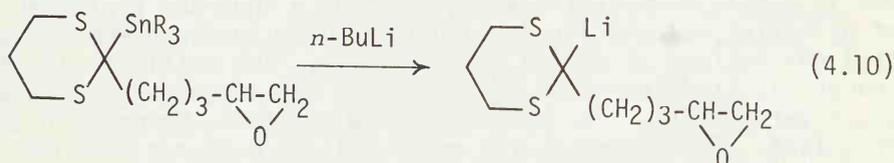
and then as an alkynyllithium, as shown in eq. 4.8 (4.19).



Transmetalation. The transmetalation reaction between two organometallic species R^1M^1 and R^2M^2 would proceed forward, if their electronegativities (EN) are $\text{EN}_{\text{R}^1} > \text{EN}_{\text{R}^2}$ and $\text{EN}_{\text{M}^1} > \text{EN}_{\text{M}^2}$. The formation of R^1M^2 between the more electronegative R^1 group and the more electropositive M^2 must be the major driving force of the reaction (eq. 4.9).



In practice, the choice of R^1 is very much limited by various factors, in particular "ate" complex formation in the case of the Group II and Group III metals. Only organotin compounds have been shown, in practice, to be useful starting compounds for the preparation of organolithiums. Although alkylolithiums are difficult to prepare by this method, it provides a convenient route to organolithiums containing allyl, benzyl, alkenyl, aryl, and cyclopropyl groups, as briefly discussed in Sects. 2.11 and 6.4.3.1. Certain proximally hetero-substituted organolithiums have also been prepared by this method, as shown in eq. 4.10 (4.20).

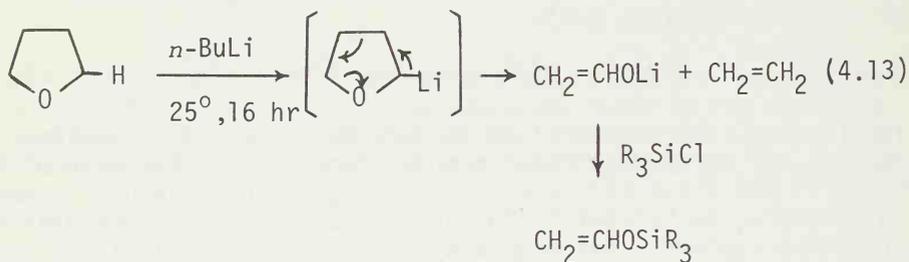


Oxidative-reductive transmetalation can also be used to prepare organolithiums. Organomercuries (eq. 4.11) and organoleads (eq. 4.12), for example, (4.21) have been used as starting materials.



These methods are particularly suited for the preparation of halogen-free organolithiums. The scope of the preparation of organolithiums by exchange reactions has been expanded in recent years to include Li-B (Sect. 5.2.3.5), Li-S (4.22 to 4.24), Li-Se (4.25, 4.26), and Li-Te (4.27) exchanges.

Other methods of preparing organolithiums include ether cleavage by lithium metal (4.28) or organolithiums (4.29), see eq. 4.13, and reactions of olefins, arenes, and acetylenes with lithium metal or organolithiums. The latter reactions are discussed in Sects. 4.3.2.5 and 4.4.1.

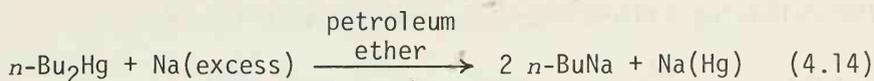


4.2.1.2 Preparation of Organosodiums and Organopotassiums

Two of the most widely used methods for preparing organolithiums, that is, oxidative metallation and metal-halogen exchange, are not well-suited for the preparation of other organoalkali metals due to highly competitive Wurtz coupling. Thus the applicability of oxidative metallation is largely limited to the preparation of aryl derivatives of sodium and potassium. The metal-halogen exchange reaction involving organosodiums and organopotassiums appears very facile. The Wurtz-coupling reaction, however, is also very fast. Consequently, the metal-halogen exchange does not provide, in practice, a useful method to prepare these organometallics.

At present, metal-hydrogen exchange reactions and transmetallation reactions represent some of the most commonly employed routes to organosodiums and organopotassiums. The former reaction, which was discussed in some detail in Sect. 2.5.1, provides a convenient route to allyl, benzyl, aryl, and alkynyl derivatives of sodium and potassium.

Perhaps the most common route to alkylsodiums and alkylpotassiums is the oxidative-reductive transmetallation reaction of alkylmercuries with sodium or potassium (eq. 4.14).



Alkylpotassiums, such as $n\text{-BuK}$, react to a considerable extent, even with petroleum ether, within a few hours at room temperature, which seriously limits the synthetic usefulness of alkylpotassiums.

4.2.2 Preparation of Organometallics Containing Mg, Zn, and Cd

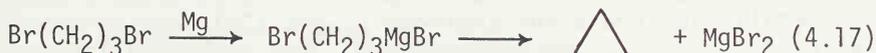
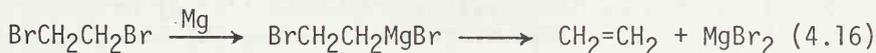
4.2.2.1 Preparation of Organomagnesiums

There are many extensive monographs and reviews on this subject, such as those by Kharasch (4.2), Coates (0.6), and Nesmeyanov (0.8). Furthermore, relatively little progress in this area has been made in recent years. Consequently, our discussion here is very brief. Of the 12 general methods of preparing organometallics, oxidative metallation (Method I) by far provides the most widely used route to organomagnesiums (eq. 4.15).



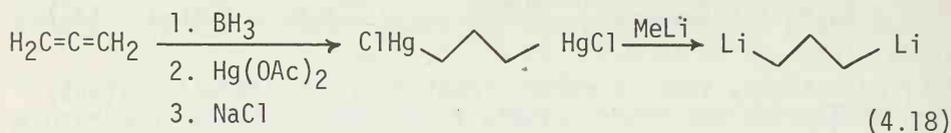
For the discovery and development of this reaction as well as the investigation of the chemistry of the organomagnesium products, that is, the Grignard reagents, V. Grignard was awarded the Nobel Prize for Chemistry in 1912.

As shown in Table 4.2, virtually all types of organomagnesium halides can be prepared by this method. Alkynylmagnesium halides are, however, usually prepared via metal-hydrogen exchange. Despite its wide applicability, many limitations also exist. Di-Grignard reagents, XMg-R-MgX , can present serious difficulties. 1,2-Dihaloethanes, such as $\text{BrCH}_2\text{CH}_2\text{Br}$, give ethylene and MgX_2 . Similarly, 1,3-dibromopropane undergoes a complex reaction with magnesium which leads to cyclopropane, propylene, and other products.

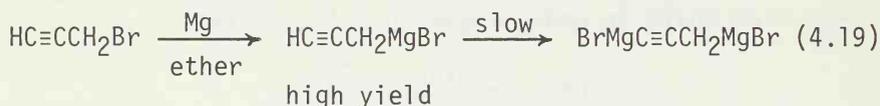


The latter problem has recently been solved by the development of

the following indirect method, see eq. 4.18 (4.30).

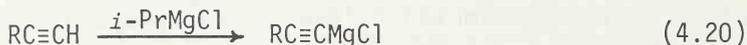


Alkenylmagnesium halides cannot be prepared readily in diethyl ether. This difficulty has been solved by using THF as a solvent (4.31). The preparation of allyl-, propargyl-, and benzylmagnesium halides is complicated by Wurtz coupling, which can be minimized, however, by very slowly adding the organic halides to magnesium suspended in a large quantity of ether. It is noteworthy that, in the conversion of propargyl bromide into propargylmagnesium bromide, abstraction of the acetylenic hydrogen atom does not occur to any serious extent (eq. 4.19).



The scope of the preparation of Grignard reagents via oxidative metallation has recently been expanded by the introduction of the active metal powder technique and the metal vapor technique (Sect. 2.1).

As the results shown in eq. 4.19 suggest, the metal-hydrogen exchange (Method V) is not a widely applicable method of preparing organomagnesiums. The active C-H compounds ($pK_a \leq 25$), however, can be converted to the corresponding Grignard reagents by treating them with highly basic Grignard reagents, such as *i*-PrMgCl, as shown in eq. 4.20.

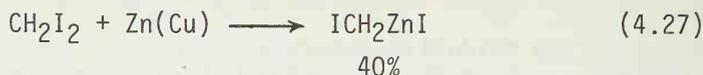


The metal-halogen exchange reaction (Method III) of Grignard reagents is generally a slow process which does not serve as a good synthetic method.

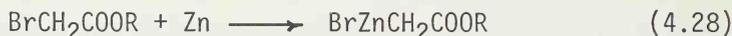
In addition to the oxidative metallation of organic halides, transmetallation reactions (Methods XI and XII) provide generally applicable routes to organomagnesiums. The transmetallation that does not involve any redox reaction generally requires organometallics that contain metals that are more electropositive than

4.26 are not complicated by Wurtz coupling.

The reaction of methylene iodide with the Zn-Cu couple gives a useful reagent for cyclopropanation, see eq. 4.27 (4.35).

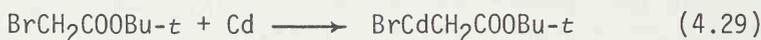


The reaction of α -bromo esters with zinc metal produces the Reformatsky reagents, see eq. 4.28 (4.34, 4.36, 4.37).

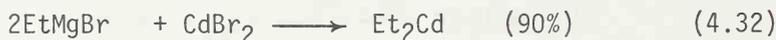
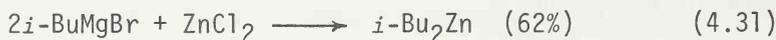
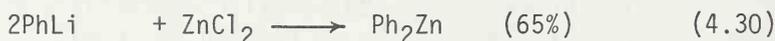


As discussed in Sect. 2.1, the use of activated zinc powder prepared by treating ZnCl_2 with potassium metal in THF permits the conversion of alkyl and aryl bromides to organozinc products, thereby expanding the scope of the oxidative metallation.

The synthetic usefulness of the oxidative metallation as a route to organocadmiums appears to be rather limited. Alkyl iodides have been reacted with cadmium metal in HMPA to give good yields of dialkylcadmiums (4.38). A cadmium analogue of the Reformatsky reagent has been prepared in DMSO (4.39).



Transmetallation. The reaction of organolithiums or Grignard reagents with zinc halides and cadmium halides, such as ZnCl_2 and CdBr_2 , represents one of the most general routes to organozincs and organocadmiums, respectively. Some typical examples are shown below.



On the other hand, the oxidative-reductive transmetallation reaction of organomercuries with zinc or cadmium is a generally sluggish equilibrium reaction, which does not appear to be of high synthetic significance.

4.3 CARBON-CARBON BOND FORMATION VIA ORGANOALKALI AND ORGANOALKALINE EARTH METALS

4.3.1 General Reaction Patterns

The great majority of selective carbon-carbon bond-forming reactions involving the use of organoalkali and organoalkaline earth metals proceed via nucleophile-electrophile interactions, which can conveniently be classified into several reaction types according to the structures of electrophiles, as summarized in Scheme 3.2 in Sect. 3.2.1.1. It is also convenient to classify organometallic nucleophiles according to the following three categories:

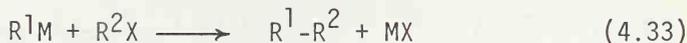
1. "Ordinary" or proximally nonfunctional organometallics, such as MeMgBr.
2. α -Hetero-substituted organometallics, such as NaCCl₃.
3. Metal enolates, such as LiO(Ph)C=CH₂.

Whether metal enolates should or should not be classified as organometallics is a matter of semantics. Since metal enolates can act as intermediates for the conversion of carbonyl compounds into α -alkylated derivatives, it is convenient to treat them as organometallic compounds regardless of their precise structures. In the following subsections, we discuss the reactions of each of the three classes of nucleophilic organometallics with several different types of electrophiles.

4.3.2 Carbon-Carbon Bond Formation via Proximally Nonfunctional Organometallics of Groups IA, IIA, and IIB Metals

4.3.2.1 Cross Coupling with Organoalkali Metals and Grignard Reagents

The cross-coupling reaction is arbitrarily defined as a process of a single carbon-carbon bond formation between two unlike carbon groups by the reaction of an organometallic species with an organic halide or a related electrophilic derivative (eq. 4.33).



The reaction represents one of the most straightforward methods of carbon-carbon bond formation. It may even be said that, if one could achieve any type of cross coupling at will, most of the problems of organic skeletal construction would be solved. Despite its inherent simplicity, however, its synthetic utility had been quite limited until recently. Until the mid-1960s, alkali

metals, lithium and magnesium in particular, had been used almost exclusively. Mainly within the past decade or so, the scope of cross coupling has been significantly broadened by the development of new cross-coupling procedures involving transition metals, particularly Cu, Ni, and Pd (Sects. 9.1 and 9.2). In this section, the scope and limitations of cross coupling involving organoalkali metals and Grignard reagents, as well as some mechanistic aspects of the reaction, are discussed.

A systematic and extensive survey of cross-coupling reactions has been presented by Mathieu and Weill-Raynal (4.40). The cross-coupling reactions of organolithiums and Grignard reagents have been reviewed by Wakefield (4.1) and Kharasch and Reinmuth (4.2), respectively.

Classification of Cross-Coupling Reactions. It is useful to classify the carbon groups to be considered in this section as follows:

1. sp^3 Hybridized carbon groups (Type I)
primary, secondary, and tertiary alkyl groups.
2. sp^3 Hybridized carbon groups (Type II)
allylic, propargylic, and benzylic groups.
3. sp^2 and sp Hybridized carbon groups (Type III)
aryl, alkenyl, and alkynyl groups.

Let us now consider coupling any two of these carbon groups. The two unlike groups may be of the same type. The information available clearly indicates that each type of cross coupling presents unique characteristics and problems and hence deserves a separate discussion. For the sake of convenience, the cross-coupling reactions may be classified arbitrarily according to the following categories:

Category I ($C_{sp^3(I)}-C_{sp^3(I)}$ coupling).

Category II ($C_{sp^3(I)}-C_{sp^3(II)}$ or $C_{sp^3(II)}-C_{sp^3(I)}$ coupling).

Category III ($C_{sp^3(II)}-C_{sp^3(II)}$ coupling).

Category IV ($C_{sp^3(I)}-C_{sp^2(sp)}$ or $C_{sp^2(sp)}-C_{sp^3(I)}$ coupling).

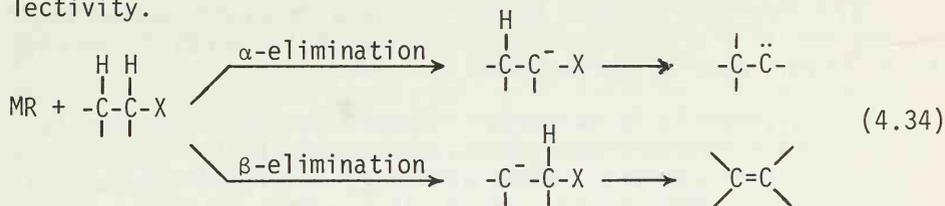
Category V ($C_{sp^3(II)}-C_{sp^2(sp)}$ or $C_{sp^2(sp)}-C_{sp^3(II)}$ coupling).

Category VI ($C_{sp^2(sp)}-C_{sp^2(sp)}$ coupling).

In the following discussions, the first carbon group of each pair refers to that of an organometallic reagent (R^1M) and the second to the carbon group (R^2) of an organic halide or a related

species (R^2X).

General Discussion of Cross Coupling with Organometallics Containing Group IA and Group II Elements. As pointed out earlier, the scope and synthetic utility of the cross coupling with organometallics containing Group IA and Group II elements are rather limited. This is mainly due to the following complications: (1) halogen-metal exchange (Sect. 4.2.1.1), (2) α - and β -elimination reactions (eq. 4.34), and (3) the general lack of chemoselectivity.



(a) Scope with respect to M. Of the Group IA and Group II metals, only lithium and magnesium have been used extensively in cross coupling. The higher alkali metals, such as sodium and potassium, are associated with several serious difficulties. Firstly, organometallics containing these alkali metals are generally much less readily available than those containing lithium and magnesium, since their preparation by either direct oxidative metallation (Sect. 2.1) or metal-halogen exchange (Sect. 2.3) is often accompanied by Wurtz homo coupling. Secondly, some of the undesirable side reactions, that is, halogen-metal exchange and α - and β -eliminations, take place more readily with the sodium and potassium derivatives than with the lithium and magnesium.

As a result, except in cases where organometallics containing sodium, potassium, and higher alkali metals are more readily available than those containing lithium and magnesium, these higher alkali metals do not generally offer any advantages over lithium and magnesium.

The nucleophilicity of organometallics containing Be, Zn, Cd, and Hg is generally too low to be of practical use. Likewise, the Group IIIA and Group IVA metals, such as B, Al, Tl, Si, Sn, and Pb, do not readily participate in the direct cross-coupling reaction. This may also be attributed to the relatively low ionicity of the M-C bond in these organometallic compounds. As discussed later, however, organoalanes and, to lesser extents, organozincs and related electrophilic organometallics have exhibited a unique capability to undergo clean substitution reactions with hindered alkyl halides. Perhaps more important is a

recent finding that organometallics containing moderately electronegative metals, such as Zn, Cd, Al, and Sn, can readily participate in nickel- or palladium-catalyzed cross coupling, as discussed in detail in Sect. 9.2.

The nucleophilicity of organometallics containing calcium and the higher Group IIA elements appears to be quite high. At present, however, relatively little is known about their synthetic capability with respect to cross coupling.

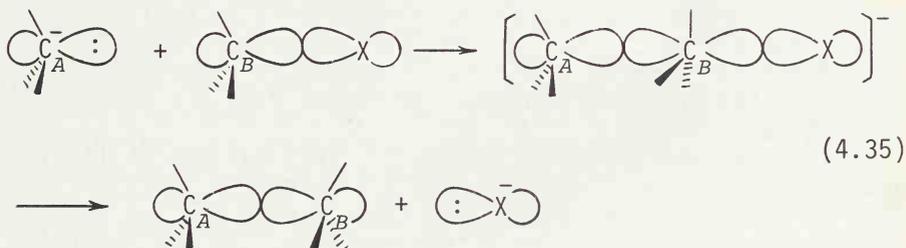
(b) Scope with respect to the R^1 and R^2 groups. Before discussing specific cross-coupling reactions, it is worth discussing the following general limitations:

1. In general, it is quite difficult to achieve successful cross coupling using highly hindered alkyl halides, such as tertiary and certain secondary alkyl halides, mainly due to competitive β -elimination. This seriously limits the scope of Category I, Category II, and Category IV cross-coupling reactions.
2. Unsaturated organic halides containing the C_{sp^2} -X and C_{sp} -X bonds, that is, aryl, alkenyl, and alkyne halides, are generally quite inert with respect to the direct carbon-carbon bond formation through their reaction with organometallics containing lithium, magnesium, and other main group metals. It is therefore either impossible or extremely difficult to achieve coupling of two unsaturated groups (Category VI) with these organometallics. The scope of Category IV and Category V cross-coupling reactions is also limited by the same fact. There are, however, a few solutions to this problem, as discussed later in this section.
3. As pointed out earlier, halogen-metal exchange presents a general difficulty. The difficulty is particularly serious when two groups to be coupled are of the same or of similar types, as in Category I and Category III coupling reactions.
4. Allylic and propargylic organolithiums and Grignard reagents can undergo facile allylic rearrangements as discussed in Sect. 4.1. This often presents difficulties regarding regio- and stereoselectivity in Category II, Category III, and Category V cross-coupling reactions.

Mechanistic Considerations. Despite the ubiquitous nature of the reaction of organolithiums and Grignard reagents with organic

halides, relatively little is known about the mechanism of the reaction in a clear-cut and definitive sense. As discussed earlier, these organometallic compounds often exist as aggregated species. Thus the actual reactive species could be either aggregated or monomeric. Ion pairing presents another major complication. Until recently, there was a widespread tendency to view highly nucleophilic organometallics such as those containing lithium, as carbanion sources and interpret the mechanism of their reaction with alkyl halides within the framework of the S_N mechanisms, involving the interaction of free carbanion species with either alkyl halides themselves or carbocationic species thereof in the rate-determining step. In principle, however, these organometallics could react with alkyl halides either as free carbanions or as ion pairs which may be either tight or solvent separated. Even in cases where the nature of the actual reactive species, with respect to aggregation and ion pairing phenomena, is known, there still exists yet another major complication. Thus the reactive species could interact with organic halides via either two-electron or one-electron transfer (free-radical intermediates). It is also possible that any given reaction may proceed by more than one mechanism operating concurrently. Because we are interested mainly in the synthetic aspects of these coupling reactions, only a few plausible mechanistic schemes proposed in recent years are briefly presented. Interested readers are referred to a recent review of this subject (4.41).

(a) S_N2 and other related ionic mechanisms. The S_N2 mechanism shown in eq. 4.35 has been proposed primarily on the basis of the stereochemistry of the reaction, that is, the inversion of the C_B group.



Some representative stereochemical data are summarized in Table 4.3. These results indicate that some reactions of allyl- and benzylmetals containing Li, Na, and Mg with certain secondary al-

kyl halides proceed with complete, or nearly complete, inversion of configuration of the R^2 group. The stereochemical results appear best accommodated by some mechanisms of the S_N2 type. It is important to note that these allyl- and benzylmetals are considerably more ionic than ordinary alkyl- and arylmetals containing the same metal atoms due to resonance stabilization. Consequently, they can better serve as sources of free carbanions required in the S_N2 mechanism depicted in eq. 4.35 than the alkyl and aryl derivatives.

Table 4.3 The Stereochemistry of the Reaction of Organometallics Containing Li, Na, and Mg with Organic Halides and Sulfonates

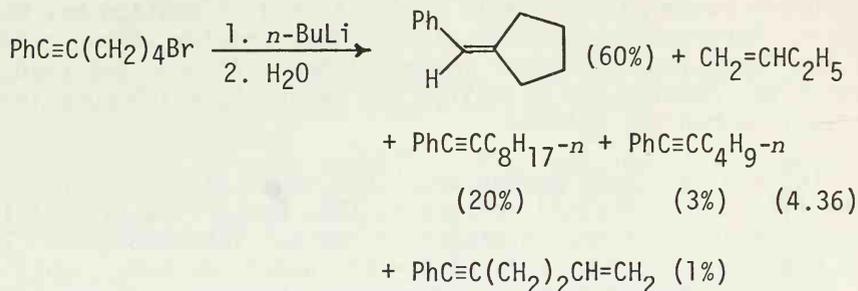
R^1M	R^2X	Yield of R^1R^2 (%)	Stereochemistry	Ref.
<i>s</i> -BuLi	2-OctI	-	80% racemization	4.42
<i>n</i> -BuLi	<i>s</i> -BuBr	37	98% racemization	4.43
<i>n</i> -BuNa	2-OctBr	35	racemization	4.44
PhLi	2-OctBr	30	racemization	4.45
AllylLi	2-OctX	59-95	>90% inversion	4.45
	(X = Cl, Br, I, or OTs)			4.46
				4.47
AllylNa	2-OctBr	83	80% inversion	4.48
AllylMgBr	2-OctBr	78	87% inversion	4.48
PhCH ₂ Li	<i>s</i> -BuBr	58	100% inversion	4.46
PhCH ₂ Li	2-OctX	-	93% inversion	4.46
	(X = Br, I, or OTs)			4.47

In marked contrast with the allyl and benzyl cases, the reactions of primary and secondary alkylmetals, as well as arylmetals containing Li, Na, and Mg, with secondary alkyl halides and sulfonates tend to proceed with extensive racemization. It is clear that an S_N2 -type mechanism cannot play a significant role in such cases.

In cases where the ionization of alkyl halides is facile for steric and electronic reasons, the S_N1 mechanism involving partial or complete racemization can compete with the S_N2 mechanism or even dominate the course of the reaction. In the reactions of allylic and propargylic halides, S_N2' and S_N1' mechanisms may also operate.

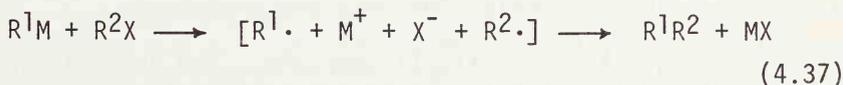
(b) One-electron transfer-radical recombination mechanism. Organoalkali metals and Grignard reagents can be readily oxidized

via one-electron transfer producing radical cationic species. On the basis of product studies a number of workers have suggested the possible intermediacy of free-radical species in the reaction of organoalkali metals and alkyl halides. For example, the reaction of 6-bromo-1-phenyl-1-hexyne with *n*-BuLi proceeds as shown in eq. 4.36 (4.49).



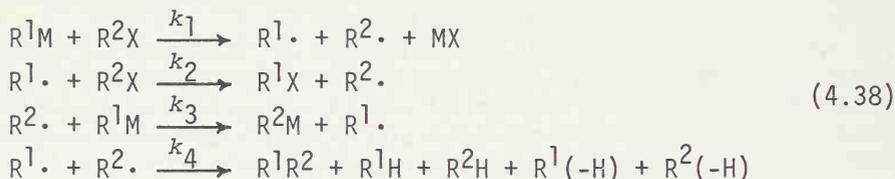
When D₂O was used in place of H₂O in the work-up, the cyclic product was only 25% deuterated. Most of the hydrogen must be incorporated into the product before the hydrolysis step. The results are in accord with a radical mechanism but not with a carbanionic mechanism, although some of the deuterated product may arise via the latter mechanism. The radical mechanism is further supported by the formation of 1-butene.

Clear-cut evidence for the existence of free-radical intermediates in reactions of this type was provided by Ward and Lawler (4.50). Thus the reaction of *n*-BuLi and *n*-BuBr produces 1-butene, which shows both emission and strongly enhanced absorption ¹H NMR signals, when the NMR measurement is made within several minutes of its formation. This abnormal NMR behavior has been called "chemically induced dynamic nuclear polarization" or CIDNP (3.1). The observed emission and enhanced absorption signals require population differences between nuclear spin energy levels that are more than 10 times greater than those of the Boltzmann population differences. The large population differences are attributable to the interaction of protons with the unpaired electrons of free-radical species. In the above example, the nuclear polarization presumably occurs in the butyl radical, which is then converted to 1-butene, which retains the imbalance of nuclear spin states decaying within several minutes via the normal spin relaxation process. The following free-radical mechanism has been proposed for the reaction (eq. 4.37).



Since then, many other examples of CIDNP observed with organolithiums and other organometallics have been reported. A few representative reagent combinations are: *n*-BuLi + *sec*-BuI (4.51), MeNa + MeI (4.53), *n*-BuMgCl + *n*-BuI (4.53), and *t*-BuMgCl + *t*-BuBr (4.53). It should be noted that the proposed free-radical mechanism is consistent with the stereochemical results, that is, extensive racemization (Table 4.3). A word of caution may be in order. Observation of CIDNP signals does provide strong evidence of the formation of radical intermediates. It does not readily permit us, however, to establish the extent to which such free-radical mechanisms operate.

(c) Radical chain mechanism. In a study of the reaction of alkyllithiums with alkyl halides by ESR, Russell (4.54) obtained direct evidence of the formation of radical intermediates. In the reaction of *n*-BuLi with RI (R = Et, *n*-Oct, or *t*-Bu), only the R• radicals arising from RI before metal-halogen exchange are observed. On the other hand, in the reaction of *n*-BuLi with certain alkyl bromides or benzyl chloride, only the signal of the *n*-Bu• radical is observed, while both possible radicals were formed in the reaction of *sec*-BuLi with EtBr and of *n*-BuLi with MeI. To accommodate these results, Russell proposes the following radical chain mechanism.

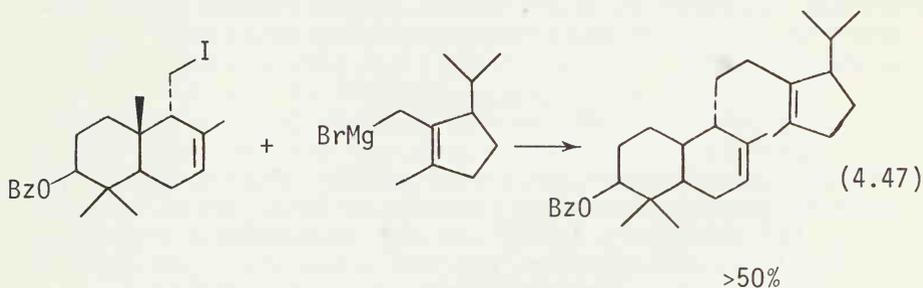
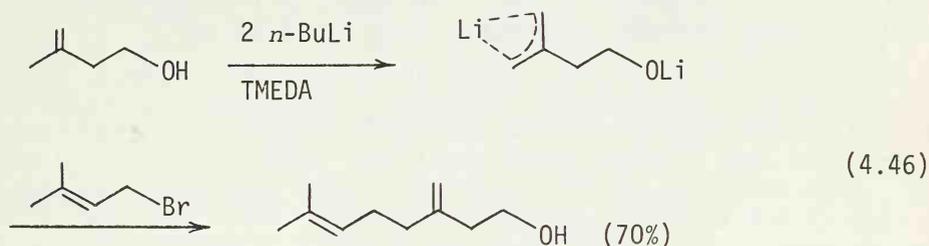
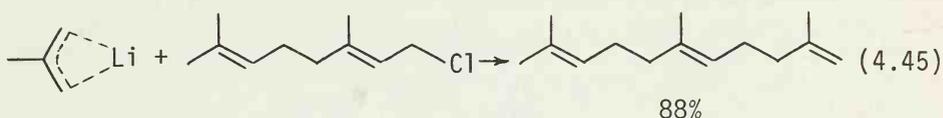


Depending on the relative magnitudes of k_2 and k_3 , either the $R^1\cdot$ or the $R^2\cdot$ radical or both radicals may be observed. It has already been mentioned that the same scheme provides a plausible mechanism for the metal-halogen exchange reaction (Sect. 2.3).

The Synthetic Utility of Cross Coupling with Organoalkali Metals and Grignard Reagents. Since each of the ten or so different classes of carbon groups tends to behave differently and present unique synthetic problems, there are a hundred or so different cases of cross coupling which should be considered separately. A detailed discussion of all of these reactions is beyond the scope of this book. Only a brief summary of the scope and a discussion of certain cases of special interest are presented.

(a) Category I (alkyl-alkyl) coupling. The generally poor alkyl-alkyl coupling reaction proceeds satisfactorily in a limit-

(4.62). The regioselectivity of the reaction of allylic sulfones appears higher than the corresponding reaction of allylic sulfides. The reductive removal of the sulfone moiety, however, is generally considerably more difficult than that of the sulfide group. In some fortunate cases, the allyl-allyl coupling has been successfully achieved with ordinary allyllithiums (4.63) and allylmagnesium halides (4.64).

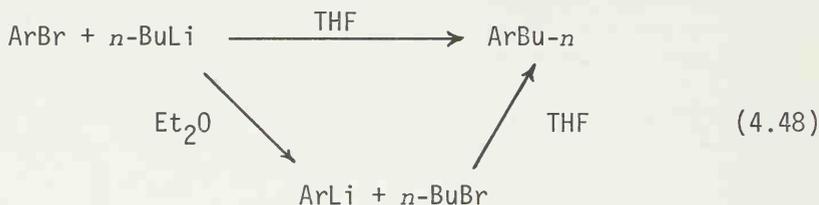


Propargylmagnesium bromide and 1-trimethylsilyl-3-lithiopropane react with allylic and benzylic halides (4.57, 4.58) as well as with propargylic halides (4.65) to give the desired cross-coupled products along with minor amounts of allenic products. These products can be further converted into 1,5-dienes.

Generally speaking, Category III cross coupling tends to be

complicated by metal-halogen exchange and allylic rearrangement. These difficulties can, in principle, be overcome by the use of α -thioorganolithium reagents. This possibility, however, does not appear to have been tested in the benzyl-benzyl case.

(d) Category IV cross coupling. The direct carbon-carbon bond formation between aryllithiums or arylmagnesium halides and aryl, alkenyl, or alkynyl halides does not usually take place under ordinary reaction conditions. This difficulty has been largely overcome by the development of cross-coupling reactions of organocuprates (Sect. 9.1). Alternatively, the difficulty could be circumvented via the charge affinity inversion operation, which, in some cases, occurs spontaneously. Thus, for example, the reaction of *n*-BuLi with various aryl halides, which gives aryllithiums via metal-halogen exchange in ether, produces *n*-butylarenes in high yields in THF. The reaction presumably proceeds via metal-halogen exchange; see eq. 4.48 (4.66).



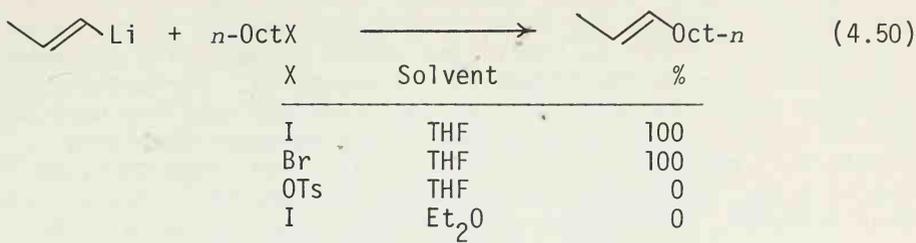
As anticipated, *sec*-BuLi or *tert*-BuLi does not give cross-coupled products, but produces aryllithiums. These results can be exploited in developing the following primary alkyl-aryl coupling procedure (4.66).



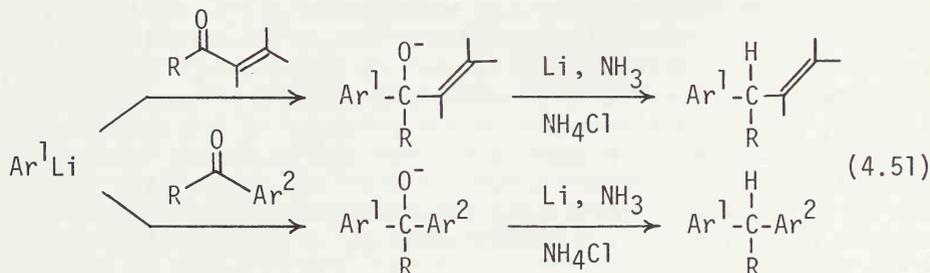
Alkenyllithiums likewise react with primary alkyl bromides and iodides to give cross-coupled products in high yields. The use of polar solvents, such as THF and DMF, is essential. Primary alkyl tosylates and chlorides are poor substrates; see eq. 4.50 (4.67). The reaction appears highly stereospecific.

The reaction of alkynylmetals containing Li, Na, K, and Mg with primary alkyl halides generally proceeds satisfactorily (4.40). Treatment of terminal acetylenes with NaNH_2 , *n*-BuLi, and *i*-PrMgCl represents a few of the most commonly used methods of generation of alkynylmetals. Here again, the use of polar solvents, such as THF, DMF, DMSO, and HMPA, is advantageous.

(e) Category V cross coupling. As in Category IV cross



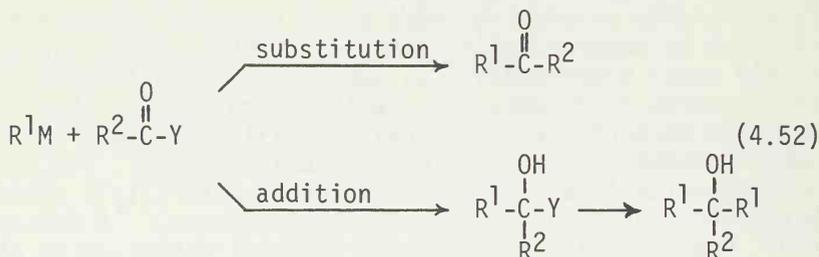
coupling, the direct carbon-carbon bond formation between allyl-, propargyl-, or benzylmetals containing alkali metals or Mg and aryl, alkenyl, or alkynyl halides does not occur readily. Here too, this problem can, in principle, be solved via charge affinity inversion. There is, however, one significant difference between Category IV and Category V coupling reactions. The products of Category V coupling contain, in the great majority of cases, highly acidic C-H bonds which could be competitively abstracted by organometallic species. Consequently, the use of highly basic organometallics, such as those containing Li, Na, and K, tends to produce less satisfactory results than those of Grignard reagents or other organometallics of lower basicity. In some favorable cases, even organoaluminums (Sect. 5.3.3.2) and organoborates (Sect. 5.2.3.3) can react with allyl, propargyl, or benzyl halides to give cross-coupled products. At present, however, organocoppers appear to be the most satisfactory class of compounds for achieving Category V cross coupling (Sect. 9.1). Another method that is highly suited for the preparation of allylated and benzylated arenes involves the reaction of aryllithiums with α,β -unsaturated and arylated carbonyl compounds, respectively, followed by reduction with lithium in NH_3 in the presence of NH_4Cl ; see eq. 4.51 (4.68). When the reactants are compatible with the reduction procedure, the desired products are formed in high yields (>80%). Unfortunately, however, alkynyl and conjugated dienyl and polyenyl groups are incompatible with the reduction procedure.



(f) Category VI- cross coupling. As discussed earlier, it is difficult to achieve the direct carbon-carbon bond formation between two sp^2 and/or sp hybridized carbon groups using organometallics containing alkali metals and magnesium. Fortunately, the problems associated with the $C_{sp^2}(sp)-C_{sp^2}(sp)$ coupling have been solved largely by the development of organocopper chemistry (Sect. 9.1) and nickel- or palladium-catalyzed cross coupling (Sect. 9.2). It is also worth mentioning that aryl-alkynyl, alkenyl-alkynyl, and alkynyl-alkynyl cross coupling can also be achieved via organoborates (Sect. 5.2.3.3).

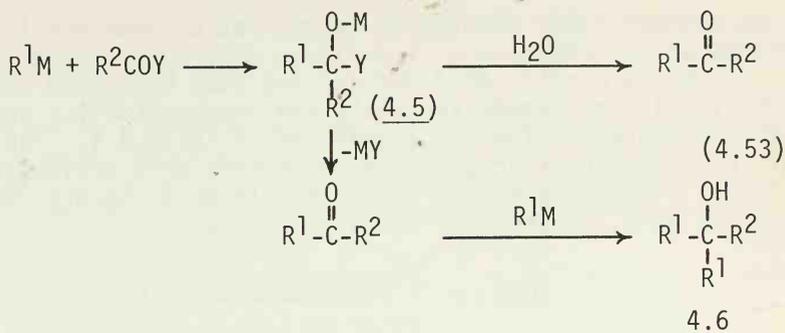
4.3.2.2 Reactions of Organoalkali Metals and Grignard Reagents with Carbonyl and Related Compounds

The reaction of organometallics with carbonyl and related compounds may arbitrarily be divided into substitution and addition reactions, as shown in eq. 4.52.



The substitution reaction produces ketones, and it may be viewed as a special case of cross coupling. The addition reaction gives various types of alcohols.

The Preparation of Ketones by the Reaction of Organometallics of Group IA and Group II Metals with Carboxylic Acids and Their Derivatives. The reaction of organometallics of Group IA and Group II metals with carboxylic acids and their derivatives appears to involve the initial attack of the carbonyl group by organometallics. If the presumed intermediate 4.5 is sufficiently stable under the reaction conditions, it can subsequently be converted into the corresponding ketone via hydrolysis. Quite often, however, 4.5 presumably decomposes under the reaction conditions, producing the ketone in the presence of the organometallic reactant (R^1M). In such cases, the corresponding tertiary alcohol tends to be formed competitively (eq. 4.53). The synthesis of the tertiary alcohol 4.6 does not present any major difficulty. Even if it is not formed readily, it can be obtained from



Y = OH, OR, SR, NR₂, CN, and so on

the ketone (R¹COR²) in a separate step. We shall therefore focus our attention on the synthesis of ketones. The early results have been reviewed by various authors (4.1, 4.2, 4.69, 4.70). Numerous recent developments, however, make it desirable to update our knowledge of this subject in this section.

As is well known, the approximate order of reactivity of various carbonyl groups toward organometallic nucleophiles is: COX (X = halogen) > COOR > CONR₂ > CN. The reaction of acyl halides and esters with organolithiums and Grignard reagents tends to produce tertiary alcohols as major products. To circumvent this difficulty, various alternate procedures have been developed. They tend to fall into either one of the following two categories:

1. Use of less reactive organometallics.
2. Use of less reactive carboxylic acid derivatives.

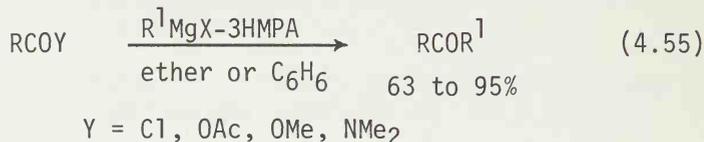
The use of organozincs and organocadmiums is well known and thoroughly reviewed; see eq. 4.54 (4.32, 4.36).



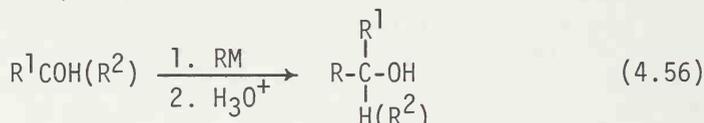
In addition to these organometallics, it has recently been shown that a variety of other organometallics react readily with acyl halides to produce ketones without the concomitant destruction of the ketones. They include organometallics containing B (Sect. 5.2.3.3), Al (Sect. 5.3.3.2), Si, and Sn (Sect. 6.4.2.1), Hg (Sect. 7.3.2.3), Cu (Sect. 9.5), Zr (Sect. 9.5), Fe (Sect. 11.3), Rh (Sect. 9.5), and Pd (Sect. 11.3). Although their relative advantages and disadvantages are not very clear, these new procedures seem to offer one distinct advantage over the use of organolithiums and Grignard reagents in that they can tolerate var-

ious electrophilic functional groups better than the lithium or magnesium procedure.

Some carboxylic acid derivatives that have been successfully employed in the ketone synthesis via organometallics containing lithium and magnesium are summarized in Table 4.4. The courses of the reaction of Grignard reagents with acyl derivatives can also be controlled by the use of highly polar aprotic solvents, such as HMPA, as shown in eq. 4.55 (4.74).



The Carbonyl Addition Reactions of Organometallics of Group IA and Group II Metals. The synthetic usefulness of the addition reactions of organometallics with acyl derivatives which lead to alcohols is limited by the fact that they produce symmetrically substituted alcohols (eq. 4.52). We shall therefore focus our attention on the addition reactions of organometallics with aldehydes and ketones (eq. 4.56).



Although the addition reaction shown in eq. 4.56 provides a reasonably general and highly useful method of carbon-carbon bond formation, the successful use of this reaction requires clear knowledge of its scope, limitations, and anticipated difficulties. There are at least three major side reactions that can complicate the desired addition reaction, (1) enolization (eq. 4.57), (2) reduction (eq. 4.58), and (3) condensation (eq. 4.59).

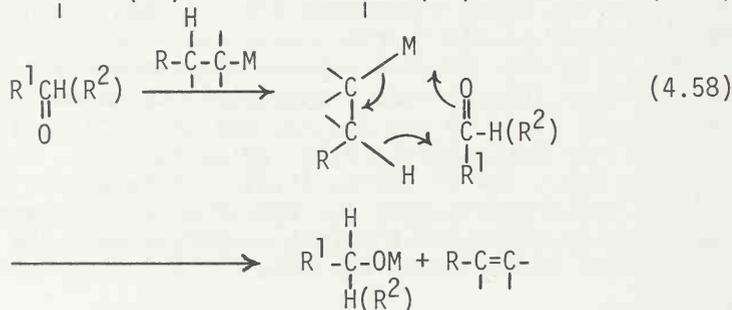
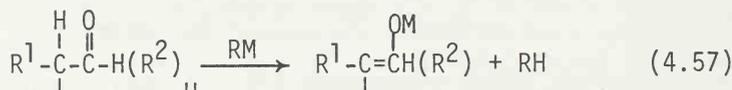
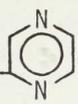
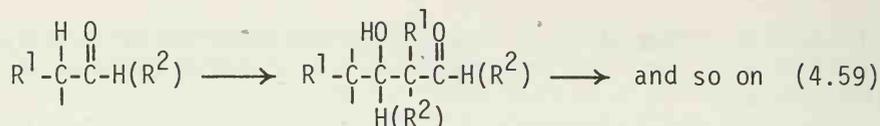


Table 4.4 Preparation of Ketones by the Reaction of Carboxylic Acid Derivatives with Organometallics Containing Lithium and Magnesium

Carboxylic Acid Derivative	Organometallic Reactant	Possible Intermediate	Typical Yields (%)	Ref.
RCOOH (RCOOLi)	R ¹ Li	$\begin{array}{l} \text{R} \diagdown \text{C} \diagup \text{OLi} \\ \text{R}^1 \diagup \text{C} \diagdown \text{OLi} \end{array}$		4.70
RCOS- 	R ¹ MgBr	$\begin{array}{l} \text{R} \diagdown \text{C} \diagup \text{S} \text{---} \text{pyridine} \\ \text{R}^1 \diagup \text{C} \diagdown \text{O} \text{---} \text{Mg} \text{---} \text{X} \end{array}$	80 to 100	4.71
RCOO- 	R ¹ MgX	$\begin{array}{l} \text{R} \diagdown \text{C} \diagup \text{O} \text{---} \text{pyridine} \\ \text{R}^1 \diagup \text{C} \diagdown \text{O} \text{---} \text{Mg} \text{---} \text{X} \end{array}$	44 to 97	4.72
RCO-CN	R ¹ MgX	$\begin{array}{l} \text{R} \diagdown \text{C} \diagup \text{CN} \\ \text{R}^1 \diagup \text{C} \diagdown \text{OMgX} \end{array}$	70 to 84	4.73
RCO-NR ₂ '	R ¹ Li	$\begin{array}{l} \text{R} \diagdown \text{C} \diagup \text{NR}'_2 \\ \text{R}^1 \diagup \text{C} \diagdown \text{OLi} \end{array}$	40 to 85	4.1
RCN	R ¹ Li	$\begin{array}{l} \text{R} \diagdown \text{C} \diagup \text{NLi} \\ \text{R}^1 \diagup \text{C} \diagdown \end{array}$	25 to 90	4.1
RCN	R ¹ MgX	$\begin{array}{l} \text{R} \diagdown \text{C} \diagup \text{NMgX} \\ \text{R}^1 \diagup \text{C} \diagdown \end{array}$		4.2

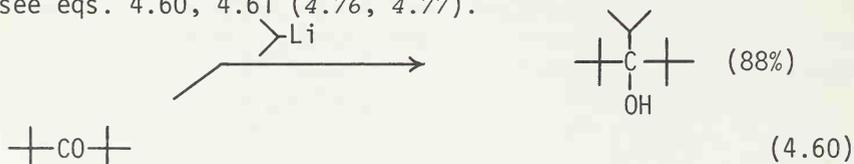


It is important to note that, in general, the Grignard reagents are far more susceptible to these side reactions than the corresponding organolithiums. The scope and limitations of the Grignard addition reaction may be indicated by the results summarized in Table 4.5 (4.75).

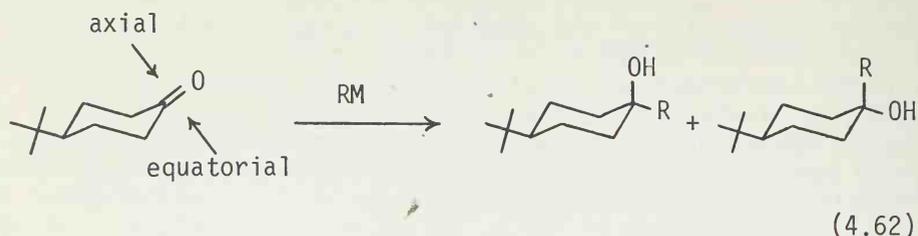
Table 4.5 The Reaction of Grignard Reagents with Diisopropyl Ketone

Grignard Reagent	Product (%)			Total
	Addition	Reduction	Enolization	
MeMgBr	95	0	0	95
EtMgBr	77	21	2	100
<i>n</i> -PrMgBr	36	60	2	98
<i>i</i> -PrMgBr	0	65	29	94
<i>i</i> -BuMgBr	8	78	11	97
<i>t</i> -BuMgBr	0	65	0	65

In contrast to the Grignard addition reaction, the scope of which is rather limited, the corresponding reaction of organolithiums is quite general, as indicated by the following examples; see eqs. 4.60, 4.61 (4.76, 4.77).

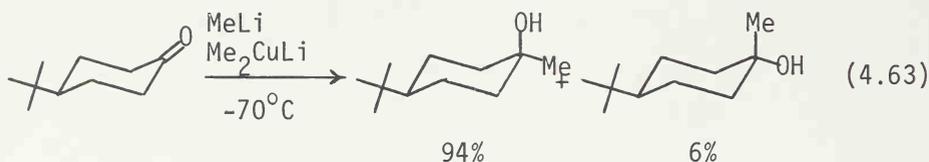


The stereochemistry of the organometallic addition to ke-



RM	Solvent	Equatorial Attack (%)	Axial Attack (%)
MeLi	Et ₂ O	65	35
PhLi	Et ₂ O	58	42
HC≡CNa	Et ₂ O-NH ₃	12	88
Me ₂ Mg	Et ₂ O	62	38
<i>t</i> -BuMgBr	Et ₂ O	100	0
Me ₃ Al (0.5 eq)	C ₆ H ₆	80	20
Me ₃ Al (2 eq)	C ₆ H ₆	17	83
2MeMgI + ZnCl ₂	Et ₂ O	38	62

important to be able to improve the isomer ratio. In this connection, recent results obtained with a mixture of MeLi and LiCuMe₂ are noteworthy; see eq. 4.63 (4.81).

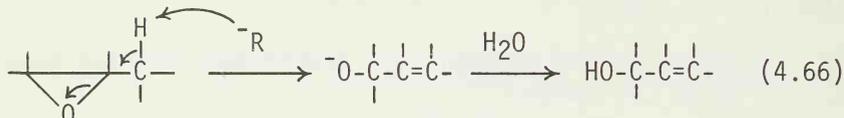


The mechanism of the carbonyl addition reaction is not very well established. Some reasonable speculations can be made, however, based on the available information. The reaction of MeLi with 2,4-dimethyl-4'-mercaptomethylbenzophenone is first order in ketone and 0.25 order in MeLi (4.82). These results are consistent with the following mechanism involving the interaction of the MeLi monomer with a ketone in the 1:1 molar ratio (eq. 4.64).

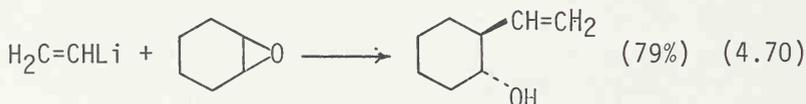
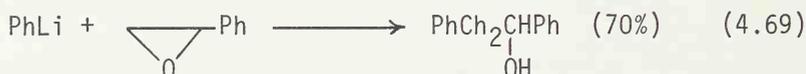
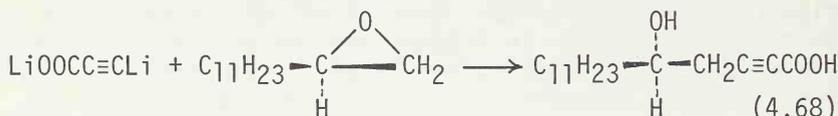
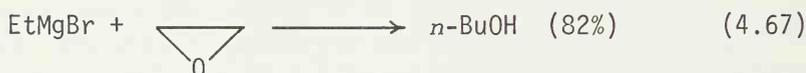
The Grignard addition reaction appears to involve a similar four-center mechanism. Although methylmagnesium halides generally add to ketones via two-electron transfer, highly hindered

In general, the reaction of epoxides with organometallics, which are more Lewis acidic than Grignard reagents, such as organozincs and organoalanes, tends to be complicated by one or more of these side reactions, although some synthetically useful reactions of organoalanes are known (Sect. 5.3.3.2).

The reaction of epoxides with organolithiums is much less prone to manifest the above-mentioned side reactions. Highly basic organolithiums, however, such as *n*-BuLi, tend to act as Brønsted bases and abstract a β -hydrogen atom, which leads to the formation of allylic alcohols (eq. 4.66).

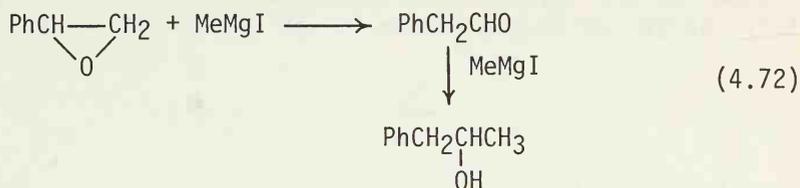
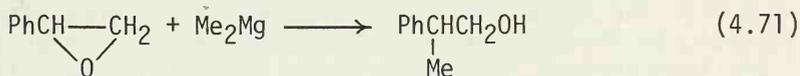


If more basic organometallics, such as those containing sodium and potassium, are used, this side reaction might be more serious, but this is not clear. Although Grignard reagents have been used most widely in the past, it appears that organolithiums and organocuprates (Sect. 9.5.2) will prove at least as useful as and probably more useful than Grignard reagents. Some representative examples of epoxide opening reactions with organometallics containing lithium and magnesium are shown below. The early results on the organomagnesium-epoxide reaction have been summarized in an extensive review (4.85).



Organolithiums tend to attack the less hindered carbon atom of the oxirane ring; see eqs. 4.68, 4.69 (4.86, 4.87). The regiochemistry of the epoxide opening reaction with Grignard re-

gents is much more complicated. With alkyl-substituted epoxides, the S_N2 opening appears to be favored. With aryl-substituted epoxides, however, the S_N1 opening has often been observed (eq. 4.71). The regiochemistry can be further complicated by the isomerization-addition path shown in eq. 4.72.



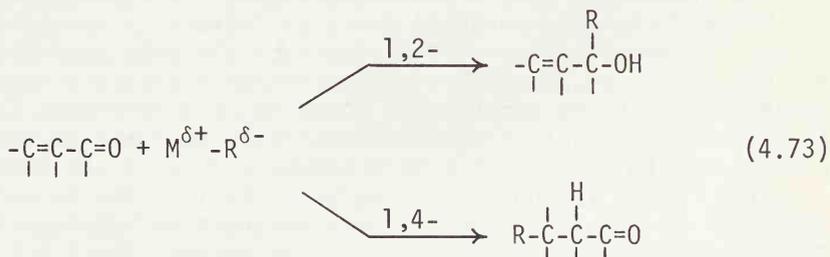
The reaction usually involves a trans opening of the oxirane ring (eq. 4.70) (4.88).

4.3.2.4 Conjugate Addition Reactions of Organometallics of Group IA and Group II Metals

α,β -Unsaturated carbonyl derivatives can act as either carbonyl or alkenyl (alkynyl) compounds.



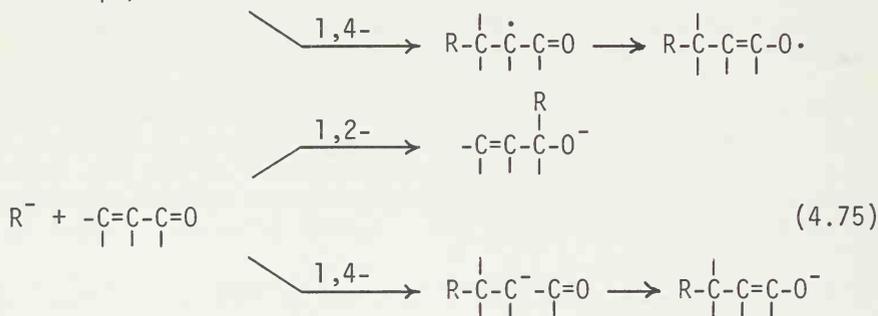
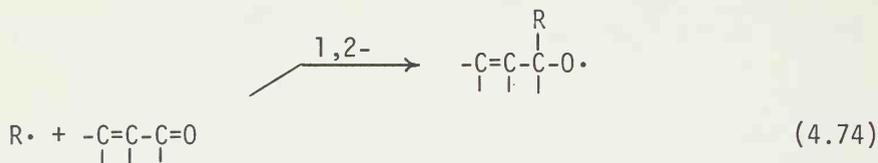
Conjugation with the carbonyl group makes the β -carbon atom a good electrophilic center. Attack at the carbonyl carbon atom by a nucleophile gives a 1,2-addition product, whereas attack at the β -carbon atom provides a 1,4-addition (or conjugate addition) product (eq. 4.73).



Despite the fact that numerous data on this reaction have been accumulated, no unifying interpretation of the available data ap-

pears to have been presented. Nonetheless, it is becoming increasingly clear that many different types of mechanisms operate in this reaction and that the 1,4/1,2 ratio is a function of a variety of factors. The following brief discussion is intended to facilitate our understanding of some factors, which presumably govern the 1,4/1,2 ratio, in a qualitative manner.

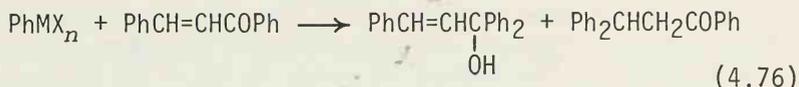
(1) The formation of the 1,4-addition product should, in general, be thermodynamically more favorable than that of the 1,2-addition product, since the former product is stabilized through delocalization of either an unpaired electron or a negative charge, while the latter is not (eqs. 4.74, 4.75).



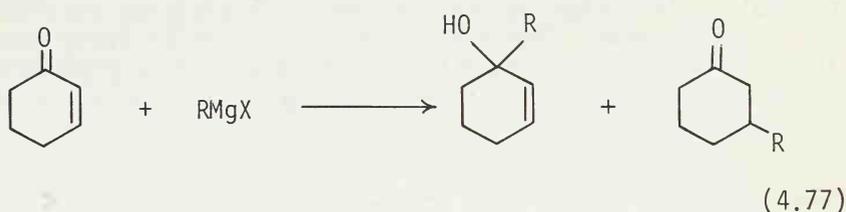
It is not surprising therefore that free-radical addition reactions of α,β -unsaturated carbonyl compounds proceed by 1,4-addition. The great majority of the known conjugate addition reactions of organoboranes (Sect. 5.2.3.3) appear to fall into this category.

(2) Based on simple considerations of electronegativity, it may be said that the carbonyl group is "harder" than the alkenyl group. As the ionicity or "hardness" of the organometallic reactants increases, the 1,2-addition, which involves a hard-hard interaction, can be kinetically more and more favored. The effect of the generation of the organometallic reactant on the 1,4/1,2 ratio is indicated by the data summarized in eq. 4.76 (4.89).

(3) There is, however, a major pitfall in the above discussion. In the reaction of 2-cyclohexenone with Grignard reagents containing Me, Et, *i*-Pr, and *t*-Bu groups, the 1,4/1,2 ratio increases as the steric requirement of the Grignard reagent increases, as summarized in eq. 4.77 (4.90).

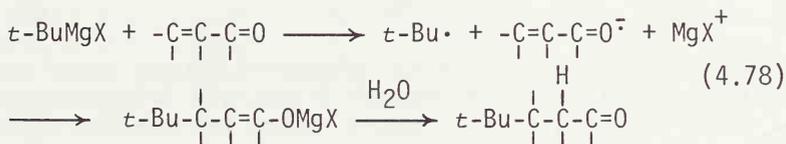


MX_n	1,2(%)	1,4(%)
Na	39	4
Li	69	13
MgBr	0	high
ZnPh	0	91



R	1,2(%)	1,4(%)
Me	38	15
Et	52	24
<i>i</i> -Pr	10	44
<i>t</i> -Bu	0	70

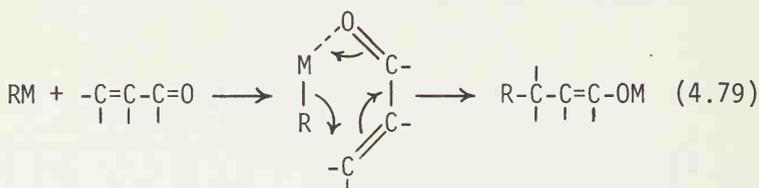
Since the ionicity of the Grignard reagent should increase as the number of Me groups increases, one might expect *t*-BuMgX to exhibit the highest 1,2/1,4 ratio. In reality, however, *t*-BuMgX does not undergo the 1,2-addition at all. The results shown in eq. 4.77 may be rationalized as follows. The high carbanionic character of *t*-BuMgX renders it highly susceptible to one-electron transfer reactions involving the intermediacy of the *t*-Bu radical which should favor the 1,4-addition over the 1,2-addition (eq. 4.78).



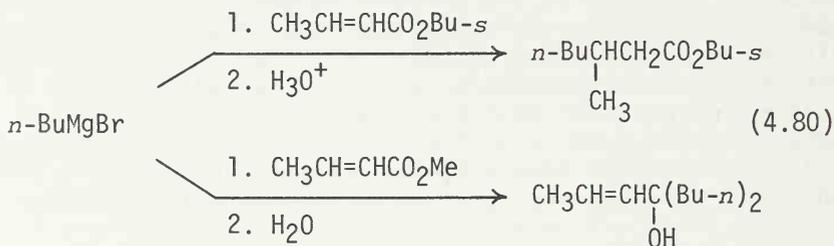
Recently it has been proposed that the conjugate addition reaction of LiCuR_2 proceeds via one-electron transfer, as discussed in Sect. 9.4.1. The mechanism shown in eq. 4.78 suggests that the extent to which a given organometal-enone reaction undergoes the 1,4-addition via one-electron transfer should be a function of the reduction potential of the enone.

(4) In cases where the formation of kinetically favored 1,2-addition products is reversible, the 1,2-addition products can be isomerized into the 1,4-addition products via equilibration. Weakly basic carbanions might participate in such a reaction. At least in some cases, the reaction of cyanoalanes with enones has been shown to proceed in this manner (Sect. 5.3.3.2).

(5) Certain highly covalent organometallics are capable of undergoing six-center pericyclic conjugate addition reactions with cisoid enones. The ready availability of an empty coordination site should facilitate such a reaction. Some conjugate addition reactions of organoboranes appear to proceed via a pericyclic mechanism (Sect. 5.2.3.3).



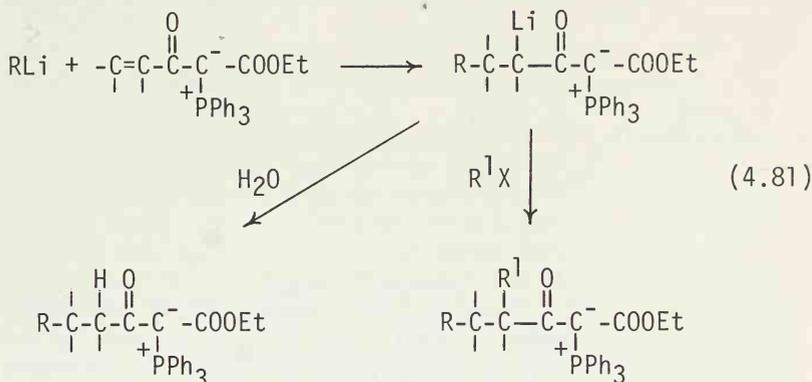
(6) The inductive, resonance, and steric effects can also affect the 1,4/1,2 ratio in a significant manner. As might be expected, steric hindrance around the carbonyl carbon and β -carbon atoms retards the 1,2- and 1,4-addition reactions, respectively. For example, whereas the *s*-butyl ester of crotonic acid undergoes predominantly a 1,4-addition reaction with *n*-BuMgBr, less hindered esters react at the carbonyl group; see eq. 4.80 (4.91).



The fact that α,β -unsaturated aldehydes almost never undergo 1,4-addition reactions with organolithiums and Grignard reagents can, at least in part, be attributed to the low steric requirements of

the formyl group.

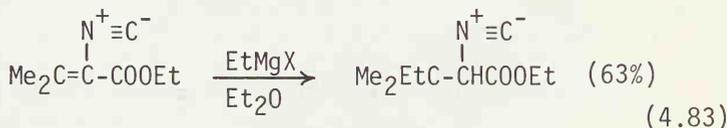
An interesting and potentially useful example of electronic manipulation of the 1,4/1,2 ratio is shown in eq. 4.81 (4.92).



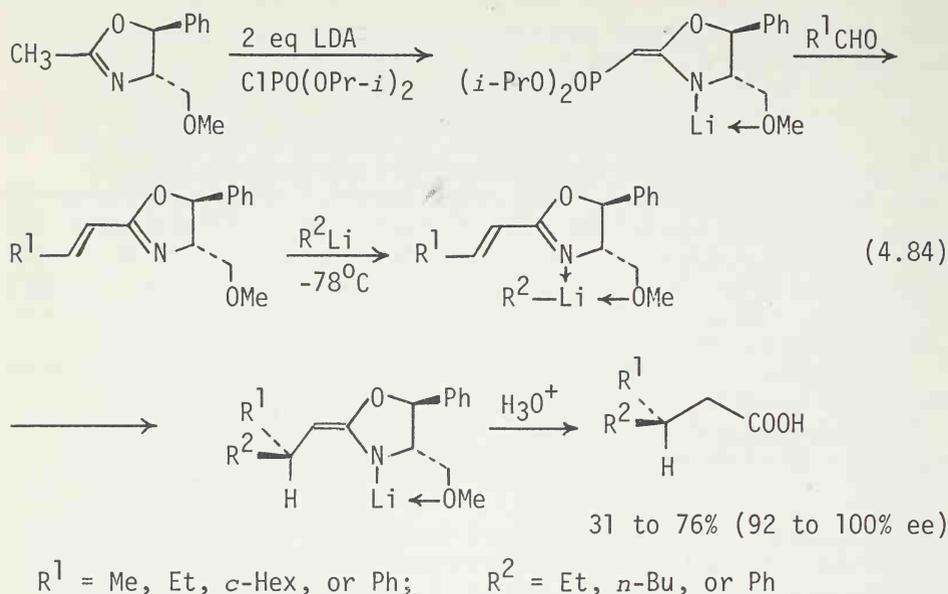
The 1,2-addition evidently is not favored by the presence of the negatively charged ylide carbon atom. The requisite enones are readily prepared as stable species by treating α,β -unsaturated acyl chlorides with $\text{Ph}_3\text{P}=\text{CHCOOEt}$. The 1,4-addition products can be treated with alcohols and concentrated HCl to remove the ylide moiety (eq. 4.82).



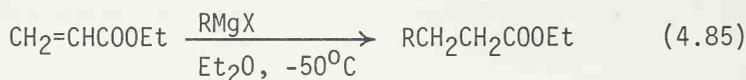
The presence of the dipolar isocyanide group in the α -position of α,β -unsaturated carbonyl compounds electronically favors the 1,4-addition; see eq. 4.83 (4.93).



Manipulation of detailed aspects of the conjugate addition reaction through modification of steric and electronic features of α,β -unsaturated carbonyl compounds, as exemplified by the two reactions shown above, seems to represent a promising area for future investigations. Especially noteworthy is a highly asymmetrical conjugate addition reaction of organolithiums with chiral vinyloxazolines which produces highly optically active products, though in modest yields; see eq. 4.84 (4.94).



(7) The 1,4/1,2 ratio can also be affected by other reaction conditions, such as the solvent used and the temperature applied. A recent report indicates that even readily polymerizable ethyl acrylate can successfully be reacted with ordinary Grignard reagents at low temperatures to produce 1,4-addition products in good yields; see eq. 4.85 (4.95).



Through manipulation of the various reaction parameters discussed above, we can now control the 1,4/1,2 ratio in many of the reactions of α,β -unsaturated carbonyl compounds with ordinary organolithiums and Grignard reagents. Even so, these reactions are not yet highly predictable and dependable. Fortunately, it has been fully established in recent years that the corresponding 1,4-addition reactions of organocoppers, especially organocuprates, are not only more dependable but generally more chemoselective than the lithium or magnesium reactions, as discussed in detail

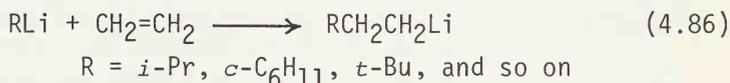
in Sect. 9.4.1. Although more limited in scope, the 1,4-addition reactions of organoborons (Sect. 5.2.3.3) and organoaluminums (Sect. 5.3.3.2), as well as certain 1,4-addition reactions catalyzed by transition metal complexes, such as $\text{Ni}(\text{acac})_2$ (Sect. 9.4.2), have exhibited a number of unique synthetic capabilities.

4.3.2.5 Reactions of Organometallics of Group IA and Group II Metals with Olefins and Acetylenes

The conjugate addition reaction of organometallics discussed in the preceding section formally involves addition of organometallics across carbon-carbon double or triple bonds. These carbon-carbon multiple bonds are electron deficient and, hence, highly activated toward nucleophiles. On the other hand, "ordinary" olefins and acetylenes are generally quite inert to organoalkali and organoalkaline earth metals under mild reaction conditions. In some special instances, however, facile carbometallation reactions of organometallics containing Group IA and Group II metals have been observed. The following reactions are worth mentioning here.

(1) Ethylene reacts with EtLi or $n\text{-BuLi}$ under pressure to give simple addition products and oligomers (4.96).

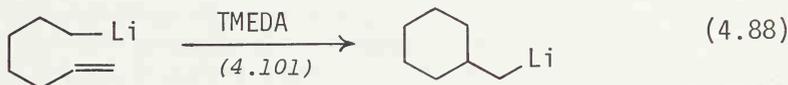
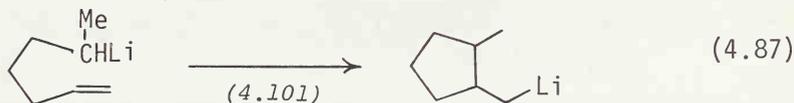
(2) The corresponding reaction of secondary and tertiary alkylolithiums turned out to be more facile than that of primary alkylolithiums; see eq. 4.86 (4.97).



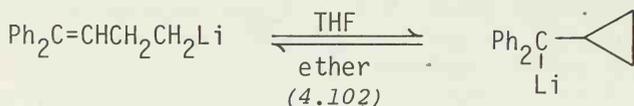
Similar reactions of $t\text{-Bu}_2\text{Zn}$ have also been reported (4.98).

(3) Although alkyl-substituted olefins are generally inert, highly strained olefins, such as cyclopropene (4.99) and norbornene (4.100), can undergo an addition reaction with alkylolithiums.

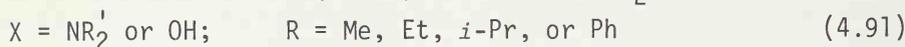
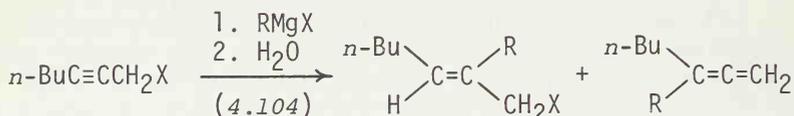
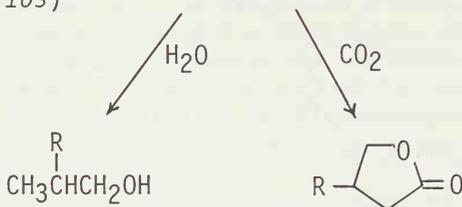
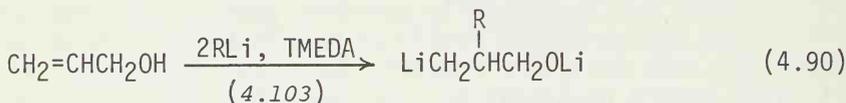
(4) The intramolecular version of the carbometallation of organoalkali and organoalkaline earth metals can be considerably more facile than the corresponding intermolecular reactions, as in the following examples.



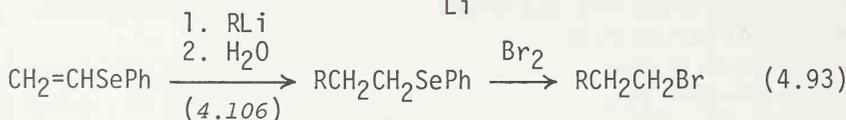
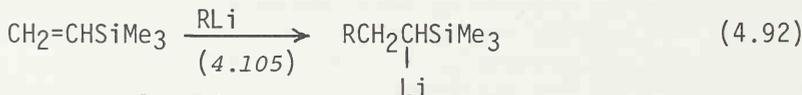
(4.89)



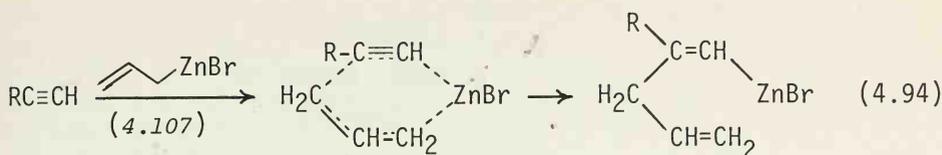
(5) Certain hetero-substituted olefins and acetylenes undergo a facile carbometallation reaction, which presumably is anchimerically assisted by the hetero substituents (eqs. 4.90, 4.91).



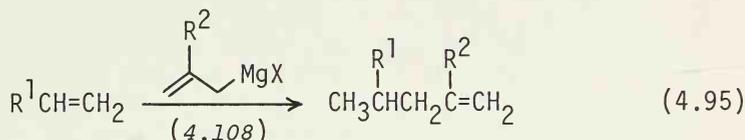
(6) Triorganosilyl and organoselenyl groups that are directly bonded to alkenyl groups activate the latter groups toward organometallics.



(7) Allylmetals containing Group IA and Group II metals can react readily with olefins and acetylenes. This reaction appears to proceed, at least partially, via six-centered transition states, such as 4.11, and appears to be closely related to the corresponding reaction of allylboranes (Sect. 5.2.3.5).

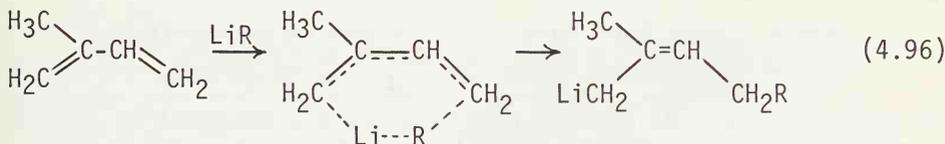


4.11



(8) The currently most important carbometallation reaction of organometallics containing Group IA and Group II metals is probably the organolithium-initiated polymerization of conjugated dienes. The discovery (4.109) that isoprene can be polymerized by organolithiums to produce *cis*-poly(isoprene), whose properties closely resemble those of natural rubbers, led to the first large-scale industrial utilization of organolithiums. The course of the polymerization is, however, very much dependent on the metal atoms of organometallic initiators and solvents. The *cis*-1,4-addition occurs only when the reaction is carried out in a nonpolar solvent using either an organolithium or lithium metal as an initiator (4.110). The scope of this book does not permit a detailed discussion of this subject. Interested readers are referred to appropriate reviews on this subject (4.111).

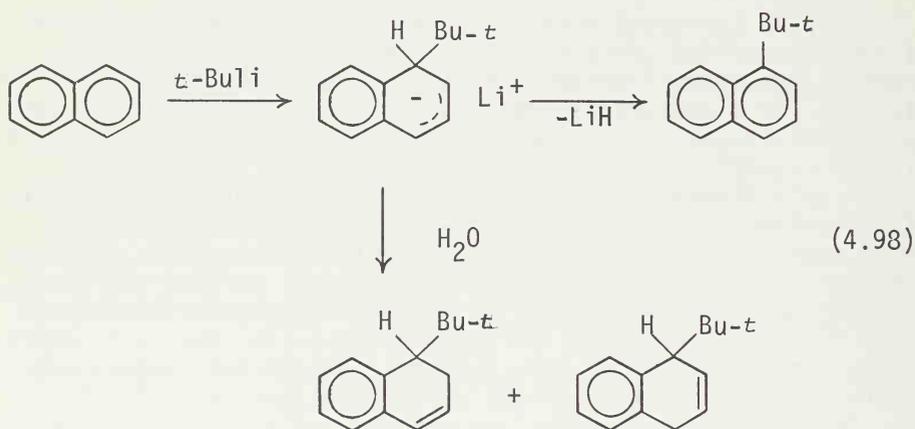
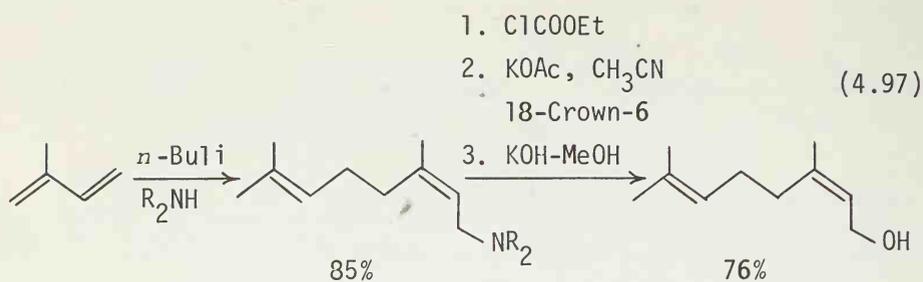
Despite numerous papers and patents, relatively little is known definitively about the mechanism of the polymerization reaction. The *cis* stereochemistry may, however, be rationalized in terms of a six-centered transition state (4.12).



4.12

The following stereo- and regioselective dimerization of isoprene; see eq. 4.97 (4.112), represents a useful modification of the polymerization reaction discussed above.

(9) Finally, the nucleophilic substitution reaction of naphthalene with *t*-BuLi has been shown to proceed via an addition-elimination mechanism; see eq. 4.98 (4.113).



4.3.3 Carbon-Carbon Bond Formation via α -Hetero-Substituted Organometallics of Group IA and Group II Metals

The acidity of a C-H bond can be significantly enhanced by either electron-withdrawing hetero substituents or carbonyl and related unsaturated groups directly bonded to the carbon atom. This makes the corresponding organometallics containing alkali and alkaline earth metals readily accessible via metal-hydrogen exchange.

Although a limited number of α -hetero-substituted organometallics, such as KCN and NaCCl₃, have been known for many decades, the synthetic significance of α -hetero-substituted organometallics in general had not been fully recognized until recently.

With the advent of highly basic reagents including organolithiums, such as *n*-BuLi, a wide variety of α -hetero-substituted organometallics have become readily available. Investigations over the past few decades have clearly established that α -hetero-substituted organometallics are a class of uniquely useful species in organic synthesis.

Hetero atoms that have been incorporated in the α -positions of these organometallics include the following: halogens (F, Cl, Br, I), oxygen (OR), sulfur (SR, SOR, SO₂R, S⁺R₂), selenium (SeR, SeOR, ⁺SeR₂), nitrogen (NO₂, ⁺N \equiv C⁻, NR(N \bar{O}), NR(CSR), NR(POX₂), NR₂, and the nitrogen atom of the C \equiv N or C=NR group), phosphorus (P⁺R₃, PR₂, PO(OR)₂, POR₂), silicon (SiR₃), tin (SnR₃), and boron (BR₂, B(OR)₂). The metal-bound carbon atom can be *sp*³ (alkyl, allyl, propargyl, benzyl), *sp*² (alkenyl, C=O, C=S, C=NR, heteroaromatic), or *sp*(CN) hybridized, and may be bonded to one, two, or three hetero atoms, which may be the same or different. Some representative examples of α -hetero-substituted organometallics containing Group IA and Group II metals are listed in Tables 4.6 to 4.12.

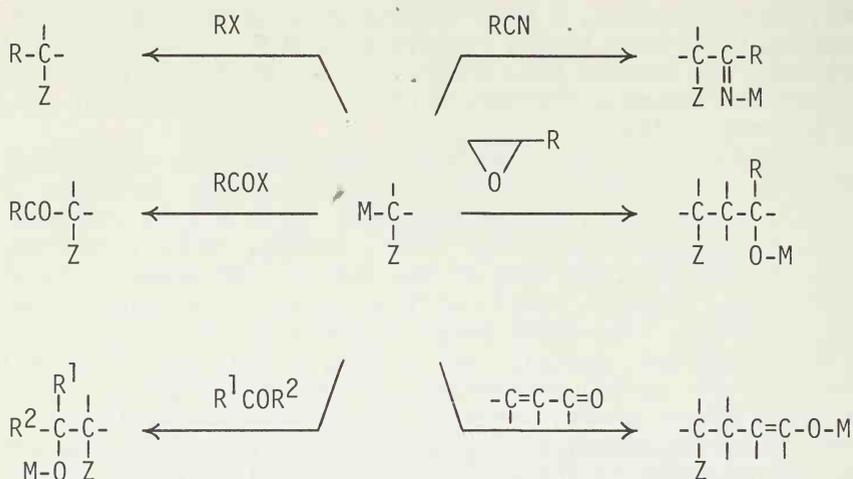
A detailed discussion of all of these α -hetero-substituted organometallics is beyond the scope of this book. Their chemistry, therefore, is discussed in a highly condensed manner in the following several sections. For further details the reader is referred to pertinent reviews and original articles cited in the following discussions.

General Reaction Patterns. The α -hetero-substituted organometallics are often thermally unstable. One of the most commonly encountered and useful modes of their decomposition is α -elimination leading to the formation of carbenes (eq. 4.99).



Organoalkali metals and organomercuries containing α -halogen atoms have proved to be especially useful as precursors to carbenes, as discussed in Sects. 4.3.3.5 and 7.3.2.2, respectively. Under appropriate conditions, α -hetero-substituted organometallics containing Group IA and Group II metals can react with various organic and inorganic electrophiles in the manner of their nonhetero-substituted analogues (Scheme 4.1). Many of the products shown in Scheme 4.1 are stable. In such cases, the presence of α -hetero substituents may not induce any transformation unique to the α -hetero substituents. In general, however, their presence permits us to achieve some synthetically useful manipulations, such as "umpolung" (Sect. 4.3.3.1) and regiochemical

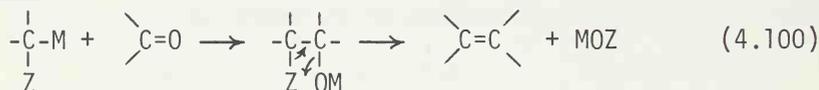
Scheme 4.1



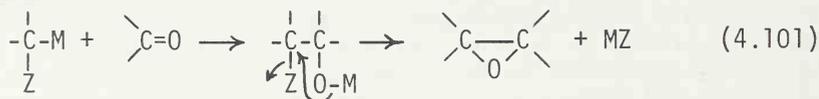
control (Sect. 4.3.3.2).

Quite frequently, the reaction of α -hetero-substituted organometallics with carbon electrophiles leads to the formation of unstable intermediates, which undergo subsequent spontaneous or assisted transformations under the reaction conditions. Some of the most useful reactions of this type are olefination (Sect. 4.3.3.3), epoxidation (Sect. 4.3.3.4), and cyclopropanation (Sect. 4.3.3.5). These reactions are shown in eqs. 4.100 to 4.102.

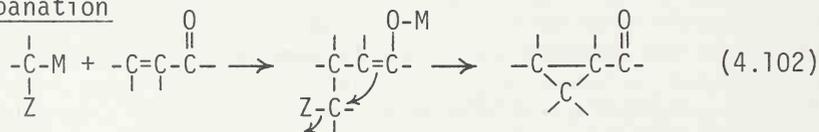
Olefination



Epoxidation



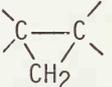
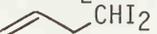
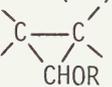
Cyclopropanation



It should also be mentioned here that α -hetero-substituted organometallics can undergo various synthetically useful carbon-

carbon forming reactions with organoboranes (Sect. 5.2.3.4).

Table 4.6 α -Halo-Substituted Organometallics of Group IA and Group II Metals^a

Compound	Method of Preparation	Use or Electrophile	Product	Ref.
LiCH ₂ Cl	<i>n</i> -BuLi (Li \rightleftharpoons Br)	Carbene precursor		4.114
LiCHCl ₂	<i>n</i> -BuLi LiN(Hex- <i>c</i>) ₂	Carbene precursor R ¹ COR ² MeCOR RCOOEt	R ¹ R ² C(OH)CHCl ₂ RMeC(Cl)CHO RCOCHCl ₂	4.115 4.116 4.117 4.118
MCCl ₃ (M = Li, Na or K)	(M \rightleftharpoons H)	Carbene precursor		4.119
LiC=C- Cl	<i>n</i> -BuLi			4.120
LiCBrHR	Li (metallation)	R ¹ COR ²	R ¹ R ² C=CHR O	4.121
LiCHBr ₂	LiN(Hex- <i>c</i>) ₂	R ¹ COR ²	R ¹ R ² C(OH)CHBr ₂	4.116
LiCBr ₂ R	LDA	R ¹ X	RR ¹ CBr ₂	4.122
LiCBr ₃	<i>n</i> -BuLi	Carbene precursor		4.123
LiC=C- Br	<i>n</i> -BuLi(Li \rightleftharpoons Br)			4.124
Li 	<i>n</i> -BuLi(Li \rightleftharpoons Br)	R ¹ COR ²	R ¹ R ² C=CH ₂ O	4.125
IMgCH ₂ I	Mg (metallation)	R ¹ COR ²	R ¹ R ² C=CH ₂	4.126
IZnCH ₂ I	Zn(Cu)			4.127
LiCHI ₂	<i>n</i> -BuLi(Li \rightleftharpoons I) LiN(Hex- <i>c</i>) ₂	 R ¹ COR ²	 R ¹ R ² C(OH)CHI ₂	4.128 4.116
LiCHOR Cl	LiTMP			4.129
KCHSC ₇ H ₇ Cl	KOBu- <i>t</i>	RCHO	RHC=O-CHSC ₇ H ₇	4.130
LiCHSOPh Cl	<i>n</i> -BuLi	R ¹ COR ²	R ¹ R ² C=O-CHSOPh	4.131

(continued...)

Table 4.6 continued

Compound	Method of Preparation	Use Electrophile	or Product	Ref.
		RCHO	RCOCH ₂ C1	4.132
$\begin{array}{c} \text{LiCHSO}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \end{array} \\ \\ \text{C1} \end{array}$	<i>n</i> -BuLi	R ¹ COR ²	$\begin{array}{c} \text{R}^1\text{R}^2\text{C}-\text{CHSO}_2\text{N} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \end{array} \\ \quad \\ \text{HO} \quad \text{C1} \end{array}$	4.133
$\begin{array}{c} \text{BrMgCHSO}_2\text{C}_7\text{H}_7 \\ \\ \text{C1} \end{array}$	EtMgBr	CO ₂	C ₇ H ₇ SO ₂ CHC1COOH	4.134
		R ¹ COR ²	$\begin{array}{c} \text{R}^1\text{R}^2\text{C}-\text{CHSO}_2\text{C}_7\text{H}_7 \\ \quad \\ \text{HO} \quad \text{C1} \end{array}$	
$\begin{array}{c} \text{LiCHPPH}_3 \\ \\ \text{C1} \end{array}$	<i>n</i> -BuLi			4.135
$\begin{array}{c} \text{LiCCl}_2\text{P(OEt)}_2 \\ \\ \text{C1} \end{array}$	<i>n</i> -BuLi	R ¹ COR ²	R ¹ R ² C=CCl ₂	4.136
$\begin{array}{c} \text{LiCBr}_2\text{P(OEt)}_2 \\ \\ \text{C1} \end{array}$	<i>n</i> -BuLi	R ¹ COR ²	R ¹ R ² C=CBr ₂	4.137
$\begin{array}{c} \text{LiCMeSiMe}_3 \\ \\ \text{C1} \end{array}$	<i>s</i> -BuLi	R ¹ COR ²	$\begin{array}{c} \text{R}^1\text{R}^2\text{C}-\text{CMeSiMe}_3 \\ \quad \\ \text{O} \end{array}$	4.138
$\begin{array}{c} \text{LiC(SiMe}_3)_2 \\ \\ \text{Br} \end{array}$		RCHO	RCH=C(Br)SiMe ₃	4.139
$\begin{array}{c} \text{LiCRCOOEt} \\ \\ \text{Br} \end{array}$	LiN(SiMe ₃) ₂	R ¹ COR ²	$\begin{array}{c} \text{R}^1\text{R}^2\text{C}-\text{CRCOOEt} \\ \quad \\ \text{O} \end{array}$	4.141
$\begin{array}{c} \text{KRCRCOOEt} \\ \\ \text{C1} \end{array}$	KOBu- <i>t</i>	R ¹ COR ²	$\begin{array}{c} \text{R}^1\text{R}^2\text{C}-\text{CRCOOEt} \\ \quad \\ \text{O} \end{array}$	4.140
(R = H, alkyl, or aryl)				
$\begin{array}{c} \text{NaCHCOPh} \\ \\ \text{C1} \end{array}$	NaOH	RCHO	$\begin{array}{c} \text{RHC}-\text{CHCOPh} \\ \quad \\ \text{O} \end{array}$	4.142
$\begin{array}{c} \text{KCHCONEt}_2 \\ \\ \text{C1} \end{array}$	KOBu- <i>t</i>	R ¹ HC=NR ²	$\begin{array}{c} \text{R}^1\text{HC}-\text{CHCONEt}_2 \\ \quad \\ \text{NR}^2 \end{array}$	4.143
$\begin{array}{c} \text{NaCHCN} \\ \\ \text{C1} \end{array}$	NaOH	R ¹ COR ²	$\begin{array}{c} \text{R}^1\text{R}^2\text{C}-\text{CHCN} \\ \quad \\ \text{O} \end{array}$	4.144
$\begin{array}{c} \text{LiCHCH=CHCOOMe} \\ \\ \text{C1} \end{array}$	KOBu- <i>t</i>	ArCHO	$\begin{array}{c} \text{ArHC}-\text{CHCH=CHCOOMe} \\ \quad \\ \text{O} \end{array}$	4.145
$\begin{array}{c} \text{NaCH} \begin{array}{c} \diagup \quad \diagdown \\ \text{C}_6\text{H}_4 \quad \text{NO}_2 \end{array} \\ \\ \text{C1} \end{array}$	NaOH	ArCHO	$\begin{array}{c} \text{ArHC}-\text{CH-Ph-NO}_2\text{-}p \\ \quad \\ \text{O} \end{array}$	4.146

^a Unless otherwise specified, the listed compounds are prepared via metal-hydrogen exchange. Metal-halogen exchange is shown by (M ⇌ X).

Table 4.7 α -Oxy-Substituted Organometallics of Group IA and Group II Metals^a

Compound	Method of Preparation	Electrophile	Product	Ref.
$\text{LiC}=\text{CH}_2$ OEt	<i>t</i> -BuLi	PhCHO	$\text{PhCHCH}=\text{CH}_2$ HO OEt	4.147
$\text{LiC}(\text{R}^1)\text{CN}$ OSiMe ₃	LDA	R^1COR^2 then H_3O^+	$\text{R}^1\text{R}^2\text{CCOCH}_3$ HO	4.148
$\text{LiCPh}(\text{CN})$ OTHP	NaH	1. R^2X 2. HCl 3. NaOH	R^1COR^2	4.149
$\text{NaCPh}(\text{CN})$ OTHP	NaH	RX then H_3O^+	PhCOR	4.150
LiCH_2OCAR O	<i>s</i> -BuLi TMEDA	RX then Hydrolysis	RCH_2OH	4.151
LiCHR^1 OR	BuLi (Li \rightleftharpoons Sn)	R^2X	$\text{R}^1\text{R}^2\text{CHOR}$	4.152
$\text{LiCHCH}=\text{CH}_2$ OSiR ₃	<i>s</i> -BuLi	R^1X	$\text{R}^1\text{CH}_2\text{CH}=\text{CHOSiR}_3$ (major)	4.153
		R^1COR^2	$\text{R}^1\text{R}^2\text{C}-\text{CHCH}=\text{CH}_2$ HO OSiR ₃	4.154
$\text{LiCHCH}=\text{CH}_2$ OBu- <i>t</i>	<i>s</i> -BuLi	RX	$\text{RCH}_2\text{CH}=\text{CHOBu-}t$ (major)	4.155
$\text{LiCHC}\equiv\text{CSMe}$ OMe	LDA	RX	$\text{MeOCH}=\text{C}=\text{CSMe}$ R	4.156
$\text{KCHSO}_2\text{C}_7\text{H}_7$ OMe	KOBu- <i>t</i>	R^1COOR	$\text{R}^1\text{COCHSO}_2\text{C}_7\text{H}_7$ OMe	4.157
$\text{Li}-\text{S} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{O} \begin{array}{c} \diagdown \\ \diagup \end{array}$		RX	$\text{R}-\text{S} \begin{array}{c} \diagup \\ \diagdown \end{array} \text{O} \begin{array}{c} \diagdown \\ \diagup \end{array}$	4.158

^a See footnote a of Table 4.6.

Table 4.8 Organometallics of Group IA and Group II Metals Containing α -Sulfur Substituents^a

Compound	Method of Preparation	Electrophile	Product	Ref.
$\text{LiCH}_2\text{SCH}_3$	<i>n</i> -BuLi TMEDA	RCHO	$\text{RCH(OH)CH}_2\text{SMe}$	4.159
LiCH_2SAr	<i>n</i> -BuLi DABCO	1. RI 2. MeI, NaI, DMF	RCH_2I	4.160
LiCR^1R^2 SPh	<i>n</i> -BuLi (Li \rightleftharpoons Se)	1. R^1COR^2 2. H_3O^+ 3. RX then base	$\text{R}^1\text{R}^2\text{C} \begin{array}{l} \diagup \text{CH}_2 \\ \diagdown \text{O} \end{array}$	4.161
$\text{LiCHCH=CR}^1\text{R}^2$ SPh	<i>n</i> -BuLi	R^3COR^4	$\text{PhSCR}^1\text{R}^2\text{CR}^3\text{R}^4$ OH	4.162
LiCHCH=CH_2 SLi	<i>n</i> -BuLi	1. $\text{R}^3\text{R}^4\text{C=CHCH}_2\text{X}$ 2. Li, EtNH ₂	$\text{R}^1\text{R}^2\text{C=CHCH}_2$ $\text{R}^3\text{R}^4\text{C=CHCH}_2$	4.61
LiCHCH=CH_2 SLi	<i>n</i> -BuLi	R^3COR^4	see eq. 4.134	4.163
LiCHCH=CH_2 SLi	<i>n</i> -BuLi	1. MgBr_2 2. R^1COR^2 3. MeI	$\text{R}^1\text{R}^2\text{C-CHCH=CH}_2$ HO SMe	4.164
LiCHPH SLi	<i>n</i> -BuLi	PhCHO	PhCHCHPh HO SH	4.165
$\text{Li} \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array}$ SPh	<i>n</i> -BuLi	R^1COR^2	$\text{R}^1\text{R}^2\text{C} \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} \diagdown \\ \diagup \end{array}$ HO SPh	4.166
LiC=CH_2 SEt	<i>s</i> -BuLi THF-HMPA	1. RBr 2. HgCl_2 , H ₂ O MeCN	RCOMe	4.167
LiC=CH_2 SEt	<i>s</i> -BuLi THF-HMPA	1. $\text{RCH} \begin{array}{l} \diagup \text{CH}_2 \\ \diagdown \text{O} \end{array}$ 2. HgCl_2 , H ₂ O MeCN	RCH=CHCOMe	4.167
LiC=CHOEt SPh	<i>t</i> -BuLi	RI	RC=CHOEt SPh	4.168
		R^1COR^2	$\text{R}^1\text{R}^2\text{C} \begin{array}{l} \diagup \text{CHOEt} \\ \diagdown \text{HO SPh} \end{array}$	4.168

Table 4.8 continued

Compound	Method of Preparation	Electrophile	Product	Ref.
	<i>n</i> -BuLi	1. RX 2. MeI, DMF	RCH ₂ I	4.169
	<i>n</i> -BuLi	1. R ² COR ³ 2. H ₃ O ⁺ 3. Δ then base		4.170
	<i>n</i> -BuLi	R ² X		4.171
	<i>s</i> -BuLi	1. RBr 2. DME, H ₂ O CaCO ₃ , Δ	RCH=CH(CH ₂) ₂ CHO	4.172
	<i>s</i> -BuLi	1. RBr 2. DME, H ₂ O, Δ	RCH ₂ CO(CH ₂) ₂ CHO	4.173
	LDA	MeI		4.174
	<i>s</i> -BuLi	1. R ² Br 2. MeI		4.175
	LDA	1. R ² X 2. Δ(PhH) 3. LDA 4. MeSSMe 5. HgX ₂ , MeCN		4.176
	LDA	RX		4.176
$\begin{pmatrix} \text{LiCH}_2\text{SOMe} \\ \text{NaCH}_2\text{SOMe} \\ \text{KCH}_2\text{SOMe} \end{pmatrix}$	<i>n</i> -BuLi NaH KOBu- <i>t</i>	E ⁺	ECH ₂ SOMe	4.177
LiCH ₂ SOC ₇ H ₇	LiNEt ₂	PhCH=NPh		4.178

Table 4.8 continued

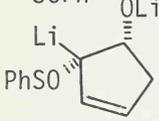
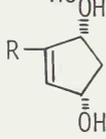
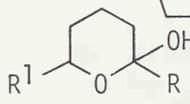
Compound	Method of Preparation	Electrophile	Product	Ref.
$\begin{array}{c} \text{LiCHR}^1 \\ \\ \text{SOPh} \end{array}$	LiICA	1. $\text{R}^2\text{CH}_2\text{X}$ 2. Δ	$\text{R}^1\text{CH}=\text{CHR}^2$ (R = Ar, SPh, SOPh, or CN)	4.179
$\begin{array}{c} \text{LiCH}_2\text{SONAr} \\ \\ \text{Li} \end{array}$	<i>n</i> -BuLi	1. RCOOR^1 2. H_2O	RCOMe	4.180
$\begin{array}{c} \text{LiCHR}^1 \\ \\ \text{SOBu-}t \end{array}$	MeLi	1. R^2COR^3 2. NCS or SO_2Cl_2	$\text{RCH}=\text{CH}_2$ $\text{R}^1\text{CH}=\text{CR}^2\text{R}^3$	4.180 4.181
$\begin{array}{c} \text{LiCHCH}=\text{CR}^1\text{R}^2 \\ \quad \\ \text{SOPh} \quad \text{OLi} \end{array}$	LDA	1. R^3X 2. $\text{P}(\text{OMe})_3$	$\text{R}^1\text{R}^2\text{CCH}=\text{CHR}^3$	4.182
	LDA	1. RX 2. HNEt_2		4.183
$\text{NaCH}_2\text{SO}_2\text{CH}_3$	$\text{NaCH}_2\text{SOCH}_3$	RCOOR^1	$\text{RCOCH}_2\text{SO}_2\text{CH}_3$	4.177a
$\text{KCH}_2\text{SO}_2\text{CH}_3$	<i>K</i> Bu- <i>t</i>	RCOOR^1	$\text{RCOCH}_2\text{SO}_2\text{CH}_3$	4.184
$\text{BrMgCH}_2\text{SO}_2\text{Ar}$	EtMgBr	RCOOR^1	$\text{RCOCH}_2\text{SO}_2\text{Ar}$	4.185
$\text{LiCH}_2\text{SO}_2\text{NMe}_2$	<i>n</i> -BuLi	RCOOR^1	$\text{RCOCH}_2\text{SO}_2\text{NMe}_2$	4.177a
$\begin{array}{c} \text{LiCHCH}_2 \\ \quad \\ \text{PhSO}_2 \quad \text{C-R} \\ \quad \quad \quad \diagup \quad \diagdown \\ \quad \quad \quad \text{O} \quad \text{O} \end{array}$	<i>n</i> -BuLi	1. R^1X 2. aq HOAc 3. base	$\begin{array}{c} \text{R}^1 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{COR} \end{array}$	4.186a
		1. R^1COOR^2 2. Al(Hg)	$\text{R CO}(\text{CH}_2)_2 \begin{array}{c} \text{C-R} \\ \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array}$	4.186b
		1.  2. Na(Hg) 3. H_3O^+		4.186c
$\begin{array}{c} \text{LiCHCH}=\text{CR}^1\text{R}^2 \\ \quad \\ \text{SO}_2\text{C}_7\text{H}_7 \end{array}$	<i>n</i> -BuLi	$\text{R}^3\text{R}^4\text{C}=\text{CHCH}_2\text{Br}$	$\text{R}^1\text{R}^2\text{C}=\text{CHCHSO}_2\text{C}_7\text{H}_7$ $\text{R}^3\text{R}^4\text{C}=\text{CHCH}_2$	4.187
$\begin{array}{c} \text{KCHC}\equiv\text{CR} \\ \\ \text{SO}_2\text{Ph} \end{array}$	<i>K</i> Bu- <i>t</i>	$\text{CH}_2=\text{CHCOOMe}$	$\text{RC}\equiv\text{C}$ 	4.188

Table 4.8 continued

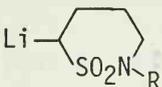
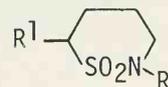
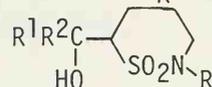
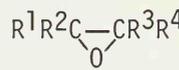
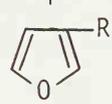
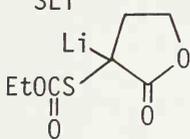
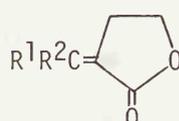
Compound	Method of Preparation	Electrophile	Product	Ref.
Li- 	<i>n</i> -BuLi	R ¹ X	R ¹ - 	4.189
		R ¹ COR ²	R ¹ R ² C- 	4.189
LiCHR Ph(O)S=NMe O LiR ¹ R ² CSR NTs	<i>n</i> -BuLi	1. R ¹ COR ² 2. Al(Hg), H ₂ O, HOAc	R ¹ R ² C=CHR	4.190
LiR ¹ R ² CSR NTs	<i>n</i> -BuLi	R ³ COR ⁴	R ¹ R ² C- 	4.191
LiCHCOOR S+	LiNH ₂	R ¹ X	R ¹ CHCOOR S+	4.192
NaCHCOOEt SPh	NaH	1. BrCH ₂ CH(OMe) ₂ 2. NaH 3. RX 4. LAH 5. TsOH, Δ		4.193
LiCHCOOEt SLi	LDA TMEDA	1. R ¹ COR ² 2. ClCOOEt	R ¹ R ² C=CHCOOEt	4.194
Li- 	LDA	R ¹ COR ²	R ¹ R ² C- 	4.195
LiCHCOOLi SPh		R ¹ COR ²	R ¹ R ² C-CHCOOH HO SPh	4.196
NaCHCOR SOMe	NaH	1. R ¹ X 2. Al(Hg)	RCOCH ₂ R ¹	4.197
		1. BrCH ₂ COOEt 2. Zn-HOAc	RCO(CH ₂) ₂ COOEt	4.198
MMeCOCH ₂ M SOPh (M = Li and/or Na)	NaH then <i>n</i> -BuLi	1. RX 2. Δ	CH ₂ =CHCOCH ₂ R	4.199

Table 4.8 continued

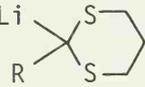
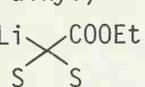
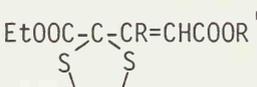
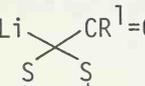
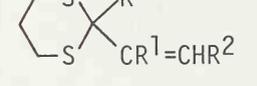
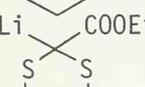
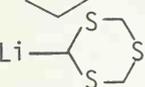
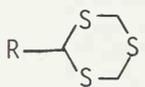
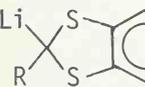
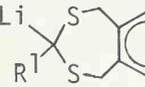
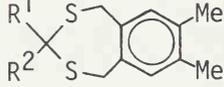
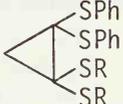
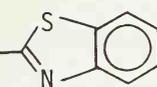
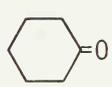
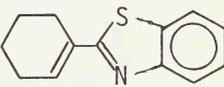
Compound	Method of Preparation	Electrophile	Product	Ref.
NaCRCOR^1 SO_2Me	NaH	$\text{BrCH}_2\text{COOEt}$	$\text{R}^1\overset{\text{R}}{\text{C}}\text{OC}=\text{CHCOOEt}$	4.200a
		1. $\text{BrCH}_2\text{COR}^2$ 2. Zn, HOAc	$\text{R}^1\text{COCHRCH}_2\text{COR}^2$	4.200b
$\text{KCHN}\equiv\text{C}$ SO_2Ar	KOBu- <i>t</i>	1. R^1COR^2 2. H_3O^+	$\text{R}^1\text{R}^2\text{CHCOOH}$	4.201a
$\text{KCHN}\equiv\text{C}$ SO_2Ar	KOBu- <i>t</i>	1. R^1COR^2 2. NaOMe MeOH reflux	$\text{R}^1\text{R}^2\text{CHCN}$	4.201b
Li  (R = H or alkyl)	<i>n</i> -BuLi	See Scheme 4.2		4.202, 4.203
Li 	LDA	$\text{RC}=\text{CHCOOR}^1$ Cl		4.204
Li 	LDA	R^3X		4.205
Li 	NaH	1. RBr 2. NBS	RCOCOOEt	4.206
Li 	<i>n</i> -BuLi	RX		4.207
Li 	<i>n</i> -BuLi	1. E^+ 2. HgO $\text{BF}_3 \cdot \text{Et}_2\text{O}$	ECOR	4.208
Li 	<i>n</i> -BuLi	R^2X		4.209
$\text{NaCH}(\text{SPh})_2$	NaNH_2	RX	$\text{RCH}(\text{SPh})_2$	4.210

Table 4.8 continued

Compound	Method of Preparation	Electrophile	Product	Ref.
$\text{NaC}(\text{SEt})_2\text{COOMe}$	NaH	$\text{CH}=\text{CHCOY}$ (Y = OR or Me)	$\text{MeOOC}(\text{SEt})_2\text{CH}_2$ YCOCH_2	4.211
$\text{LiCHSC}(\text{S})\text{NMe}_2$ SMe	<i>n</i> -BuLi	1. RI 2. HgX_2 , MeOH	$\text{RCH}(\text{OMe})_2$	4.212
LiCR^1SOMe SMe ($\text{R}^1 = \text{H}$ or alkyl)	<i>n</i> -BuLi or LDA	1. E^+ 2. H_3O^+	ECOR^1	4.213
LiCR^1SOEt SEt ($\text{R}^1 = \text{H}$ or alkyl)	<i>n</i> -BuLi or LDA	1. E^+ 2. H_3O^+	ECOR^1	4.214
$\text{LiC}(\text{SPh})_3$	<i>n</i> -BuLi	RI R^1COR^2	$\text{RC}(\text{SPh})_3$ $\text{R}^1\text{R}^2\text{CC}(\text{SPh})_3$ HO	4.215
		$\text{H}_2\text{C}=\text{C}(\text{SR})_2$		4.215
		$\text{R}^1\text{CH}=\text{CHCOR}^2$	$(\text{PhS})_3\text{CR}^1\text{CHCH}_2\text{COR}^2$	4.216
Li  <i>n</i> -BuLi	<i>n</i> -BuLi			4.217

^a See footnote a of Table 4.6.

Table 4.9 Organometallics of Group IA and Group II Metals Containing α -Selenium Substituents^a

Compound	Method of Preparation	Electrophile	Product	Ref.
LiCR^1R^2 SeR	<i>n</i> -BuLi ($\text{Li} \rightleftharpoons \text{Se}$)	R^3COR^4	$\text{R}^1\text{R}^2\text{C}-\text{CR}^3\text{R}^4$ RSe OH	4.218

(continued...)

Table 4.9 continued

Compound	Method of Preparation	Electrophile	Product	Ref.
$\begin{array}{c} \text{LiCR}^1\text{CH}_2\text{R}^2 \\ \\ \text{Se(O)R} \end{array}$	LDA	<ol style="list-style-type: none"> R^3COR^4 HOAc heat R^3X	$\begin{array}{c} \text{R}^2\text{CH}=\text{CR}^1\text{CR}^3\text{R}^4 \\ \\ \text{OH} \\ \text{R}^1\text{R}^3\text{CCH}_2\text{R}^2 \\ \\ \text{Se(O)R} \end{array}$	4.219
$\begin{array}{c} \text{LiCR}^1\text{CH}=\text{CR}^2\text{R}^2 \\ \\ \text{SePh} \end{array}$		<ol style="list-style-type: none"> RX $\text{H}_2\text{O}_2, \text{Py}$ 	$\begin{array}{c} \text{RR}^1\text{C}=\text{CHCR}^2\text{R}^3 \\ \\ \text{OH} \end{array}$	4.220
$\begin{array}{c} \text{LiCHC}\equiv\text{CLi} \\ \\ \text{SePh} \end{array}$	LDA	<ol style="list-style-type: none"> RX E^+ 	$\begin{array}{c} \text{RCHC}\equiv\text{CE} \\ \\ \text{SePh} \end{array}$	4.221
$\begin{array}{c} \text{LiCHSiMe}_3 \\ \\ \text{SePh} \end{array}$		<ol style="list-style-type: none"> RCH_2X H_2O_2 	RCH_2CHO	4.222

^a See footnote a of Table 4.6.

Table 4.10 Organometallics of Group IA and Group II Metals Containing α -Nitrogen Substituents^a

Compound	Method of Preparation	Electrophile	Product	Ref.
$\text{LiCH}_2\text{N(NO)R}$	LDA	R^1COR^2	$\begin{array}{c} \text{R}^1\text{R}^2\text{CCH}_2\text{N(NO)R} \\ \\ \text{OH} \end{array}$	4.223
		R^1X	$\text{R}^1\text{CH}_2\text{N(NO)R}$	4.223
$\begin{array}{c} \text{LiCHPh} \\ \\ \text{MeNPO(NMe}_2)_2 \end{array}$	<i>n</i> -BuLi	RX	$\begin{array}{c} \text{PhRHCNPO(NMe}_2)_2 \\ \\ \text{Me} \end{array}$	4.224
$\begin{array}{c} \text{LiCHCH}=\text{CH}_2 \\ \\ \text{NMePh} \end{array}$	<i>n</i> -BuLi	RX	$\begin{array}{c} \text{CH}=\text{CHCH}_2\text{R} \\ \\ \text{NMePh} \end{array}$	4.225
$\begin{array}{c} \text{LiCHCH}=\text{CH}_2 \\ \\ \text{N} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \end{array}$	<i>s</i> -BuLi	RX	$\begin{array}{c} \text{RCHCH}=\text{CH}_2 \\ \\ \text{N} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \\ \diagup \quad \diagdown \\ \text{C} \quad \text{C} \\ \diagdown \quad \diagup \\ \text{C} \quad \text{C} \end{array}$	4.226
$\begin{array}{c} \text{LiCHR}^1 \\ \\ \text{NO}_2 \end{array}$		<ol style="list-style-type: none"> $\begin{array}{c} \text{CH}_2 \\ \\ \text{C}=\text{C}-\text{R}^2 \\ \\ \text{O} \end{array}$ 	$\begin{array}{c} \text{R}^1\text{C}(\text{CH}_2)_2\text{CR}^2 \\ \quad \\ \text{O} \quad \text{O} \end{array}$	4.227

Table 4.10 continued

Compound	Method of Preparation	Electrophile	Product	Ref.
		2. TiCl_3		
		1.		4.228
LiCHR^1 $\text{N}\equiv\text{C}$		2. O_3 , base		
		$\text{R}^2\text{R}^3\text{C}=\text{NR}^4$		4.229
$\text{LiC}=\text{CR}^1\text{R}^2$ $\text{N}\equiv\text{C}$	<i>n</i> -BuLi	E^+	$\text{EC}=\text{CR}^1\text{R}^2$ $\text{N}\equiv\text{C}$	4.230
LiCR 	$\text{C}_8\text{H}_{17}\text{N}\equiv\text{C}$ and RLi	PhCHO	PhCHCOR OH	4.231
			$\text{R}^1\text{CHCH}_2\text{COR}$ OH	4.231
$\text{LiC}=\text{O}$ $\text{N}(\text{Pr}-i)_2$	LDA	$\text{Ph}_2\text{C}=\text{O}$	$\text{Ph}_2\text{CCON}(\text{Pr}-i)_2$ HO	4.232
Li -	<i>n</i> -BuLi			4.217

^a See footnote a of Table 4.6.

Table 4.11 Organometallics of Group IA and Group II Metals Containing α -Phosphorus Substituents^a

Compound	Method of Preparation	Electrophile	Product	Ref.
NaCRCOOEt $\text{PO}(\text{OEt})_2$	NaH	R^1COR^2	$\text{R}^1\text{R}^2\text{C}=\text{CRCOOEt}$	4.233
NaCHCN $\text{PO}(\text{OEt})_2$	NaH	R^1COR^2	$\text{R}^1\text{R}^2\text{C}=\text{CHCN}$	4.234

Table 4.11 continued

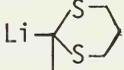
Compound	Method of Preparation	Electrophile	Product	Ref.
$\text{LiCHCH=CR}^1\text{R}^2$ PO(OEt)_2	<i>n</i> -BuLi	1. R^3X 2. LiAlH_4	$\text{R}^1\text{R}^2\text{CHCH=CHR}^3$	4.235
LiCR(SMe) PO(OEt)_2	<i>n</i> -BuLi	R^1CHO	$\text{R}^1\text{CH=CR(SMe)}$ $\downarrow \text{HgCl}_2, \text{H}_2\text{O}, \text{CH}_3\text{CN}$ $\text{R}^1\text{CH}_2\text{COR}$	4.236
LiCHSOMe PO(OEt)_2	<i>n</i> -BuLi	R^1COR^2	$\text{R}^1\text{R}^2\text{C=CHSOMe}$	4.237
LiCHSO_2Ar P(OEt)_2	<i>n</i> -BuLi	R^1COR^2	$\text{R}^1\text{R}^2\text{C=CHSO}_2\text{Ar}$	4.238
LiCR(SePh) PO(OEt)_2	<i>n</i> -BuLi	R^1COR^2	$\text{R}^1\text{R}^2\text{C=CR(SePh)}$	4.239

^a See footnote a of Table 4.6.

Table 4.12 Organometallics of Group IA and Group II Metals Containing α -Silicon Substituents^a

Compound	Method of Preparation	Ref.	Compound	Method of Preparation	Ref.
LiCHPh SiMe_3	<i>n</i> -BuLi	4.240	LiCHP(S)Ph_2 SiMe_3	<i>n</i> -BuLi	4.240
LiCHR^1 SiR_3	<i>n</i> -BuLi ($\text{Li} \rightleftharpoons \text{Se}$)	4.241	LiCHPO(OEt)_2 SiMe_3	<i>n</i> -BuLi	4.252
$\text{LiCHCH}_2\text{R}^1$ SiR_3	$\text{R}_3\text{SiCH=CH}_2$ +RLi	4.242	$\text{NaCH(SiMe}_3)_2$	NaOMe HMPA	4.250
LiCHCH=CH_2 SiMe_3	<i>n</i> -BuLi	4.243	$\text{LiC(SiMe}_3)_3$	LiOMe, MeLi	4.250 4.244
LiC=CH_2 SiMe_3	<i>t</i> -BuLi ($\text{Li} \rightleftharpoons \text{Br}$)	4.244	$\text{LiCR(SiMe}_3)_2$		4.251

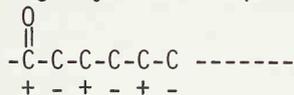
Table 4.12 continued

Compound	Method of Preparation	Ref.	Compound	Method of Preparation	Ref.
LiCHCOOR^1 SiR_3	LDA	4.245	LiCHSMe SiMe_3	<i>n</i> -BuLi	4.252
LiCHCOOLi SiMe_3		4.246	LiCHSPh SiMe_3	<i>n</i> -BuLi	4.253
LiCHCN SiMe_3		4.247	LiCHSOPh SiMe_3	<i>n</i> -BuLi	4.240
LiCHCONR_2 SiMe_3	BuLi or LDA	4.248	$\text{LiC}(\text{SR})_2$ SiMe_3	<i>n</i> -BuLi	4.254
LiCMeCH=NR SiMe_3	LDA	4.249	Li 	<i>n</i> -BuLi	4.255
LiCHPPH_2 SiMe_3	<i>n</i> -BuLi	4.240			

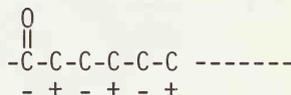
^a See footnote a of Table 4.6.

4.3.3.1 "Umpolung" -- Charge Affinity Inversion

The carbonyl and neighboring carbon atoms of carbonyl compounds normally act as either nucleophilic or electrophilic centers as shown in 4.13. This charge affinity pattern can be reversed, as shown in 4.14 through the use of various "masked" carbonyl compounds. The charge affinity inversion operation has been termed "umpolung" by Seebach (4.256).



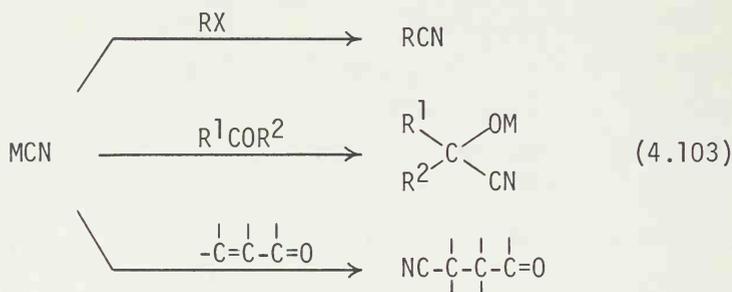
4.13



4.14

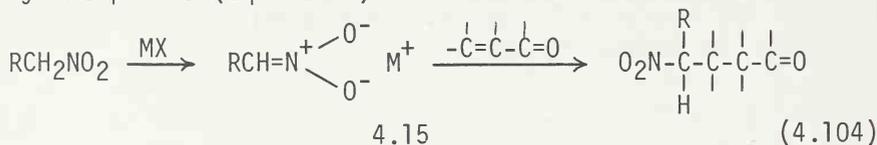
Masked Carbonyl Compounds or Acyl Anion Equivalents. Our brief discussion of this important subject may be supplemented by referring to extensive reviews by Seebach (4.256, 4.257) and Lever (4.258).

(a) Cyanides, nitronates, and other classical acyl anion equivalents. For many decades, metal cyanides and metal nitronates have been used as acyl anion equivalents. Note that these compounds are, in a formal sense, α -hetero-substituted organometallic species. A few representative carbon-carbon bond-forming reactions of metal cyanides are shown in eq. 4.103. The cyano group can be readily converted into various carbonyl groups either by reduction or by hydrolysis.

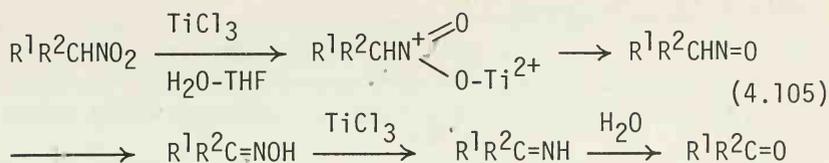


One practical difficulty in the use of alkali metal cyanides, such as NaCN and KCN, lies in their extreme insolubility in typical organic solvents. It has, however, been at least partially solved by the development of (1) polar aprotic solvents, such as DMF, DMSO, and HMPA, and (2) phase transfer catalysts (4.259). The formation of cyanohydrin can be facilitated by Me_3SiCN (4.260), and various difficulties encountered in the conjugate addition reaction of alkali metal cyanides can be overcome by Et_2AlCN , as discussed in Sect. 5.3.3.2.

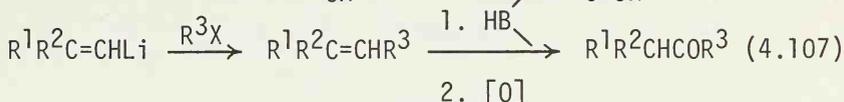
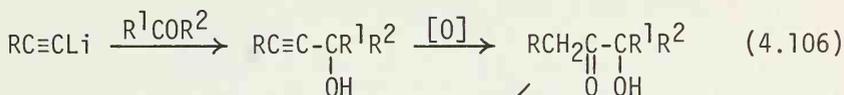
As might be expected from the relatively high acidity of nitroalkanes (e.g., $\text{p}K_a$ of $\text{CH}_3\text{NO}_2 = 10$), metal nitronates (4.15) readily undergo conjugate addition reactions with α,β -unsaturated carbonyl compounds (eq. 4.104).



The δ -carbonyl nitroalkane products can be converted into 1,4-dicarbonyl compounds by various methods. The classical Nef reaction (4.261), which involves treatment with NaOH followed by mineral acids, is often incompatible with the carbonyl and other functional groups present in the products. Consequently, a number of alternate procedures have been developed. Treatment of nitroalkanes with aqueous TiCl_3 (4.227), which presumably proceeds as shown in eq. 4.105, appears particularly promising.

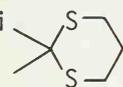
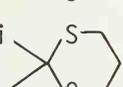
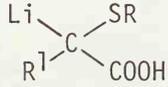
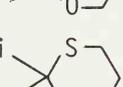
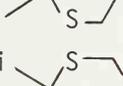
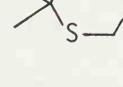
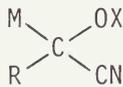


Although no detailed discussion is intended, it may be pointed out here that alkynylmetals and alkenylmetals can also act as acyl anion equivalents, as exemplified by eqs. 4.106 and 4.107.



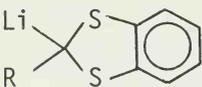
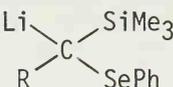
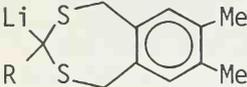
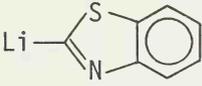
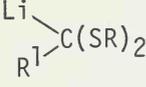
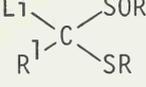
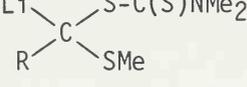
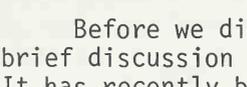
(b) Other α -hetero-substituted organometallics used as acyl anion equivalents. Extensive investigations pioneered by Corey, Seebach, and others over the past decade or two have established that a wide variety of α -hetero-substituted organometallics can serve as acyl anion equivalents. Some representative examples are shown in Table 4.13.

Table 4.13 Some Representative Acyl Anion Equivalents

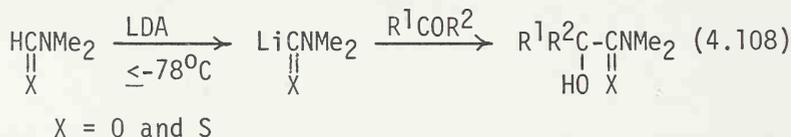
Compound	Ref.	Compound	Ref.
Li 	4.202	LiC(SPh) ₃	4.215
R 	4.203	Li 	4.196
Li 	4.158	LiC=CH ₂	4.167
R 	4.204	SEt	
Li 	4.207	LiC=CH ₂	4.148
R 		OEt	
		M 	4.150

(continued...)

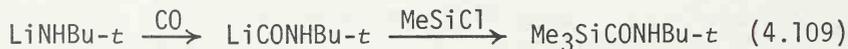
Table 4.13 continued

Compound	Ref.	Compound	Ref.
	4.208		4.222
	4.209	LiCH ₂ N(NO)R	4.223
	4.217	LiC=NR R ¹	4.231
	4.210	LiC=CH ₂ SiMe ₃	4.244
	4.213		
	4.214		
	4.212		

Before we discuss the chemistry of masked carbonyl anions, a brief discussion of "unmasked" carbonyl anions is presented here. It has recently become feasible to deprotonate nonenolizable formyl derivatives to give metal carbonylates of alkali metals. Thus Schöllkopf (4.262) and Seebach (4.263) have treated DMF and its thio derivative, respectively, with LDA at low temperatures (<-78°C) and obtained unstable lithio derivatives which undergo carbonyl addition reactions (eq. 4.108).



Alternatively carbonylation of certain lithium amides has provided products which behave as lithioformamides, as shown in eq. 4.109 (4.264).

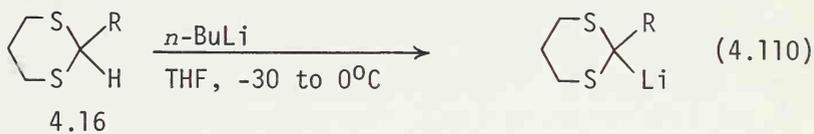


While these metal carbonylates of main group metals are interest-

ing, their synthetic values are severely limited due to their extreme instability. On the other hand, acyltransition metal compounds, such as $\text{NaRCOFe}(\text{CO})_4$ and $\text{LiRCONi}(\text{CO})_3$, have proved to be highly useful intermediates, as discussed in detail in Sect. 11.2.

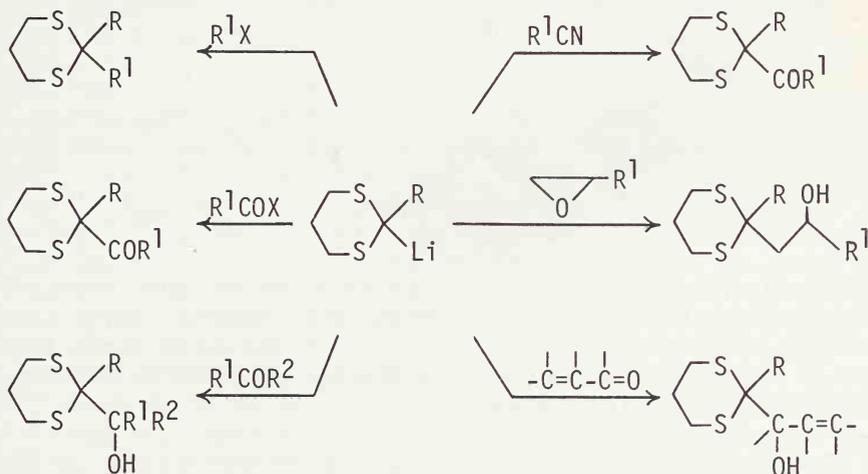
Dithiane and related cyclic and acyclic S,S-acetal derivatives. Dithiane (4.16) is probably the most widely used acyl anion equivalent. Since its use as an acyl anion equivalent was reported by Corey and Seebach (4.202a) in 1965, it has been applied to the synthesis of a wide variety of organic compounds including natural products. These results have been extensively reviewed by Seebach (4.203).

Conversion of dithiane ($\text{p}K_a = 31$) and its organo-substituted derivatives into the corresponding 2-lithiodithianes is usually achieved by treating them with $n\text{-BuLi}$ in THF or other organic solvents at -30 to 0°C (eq. 4.110).



Some representative reactions of 2-lithiodithiane derivatives are summarized in Scheme 4.2.

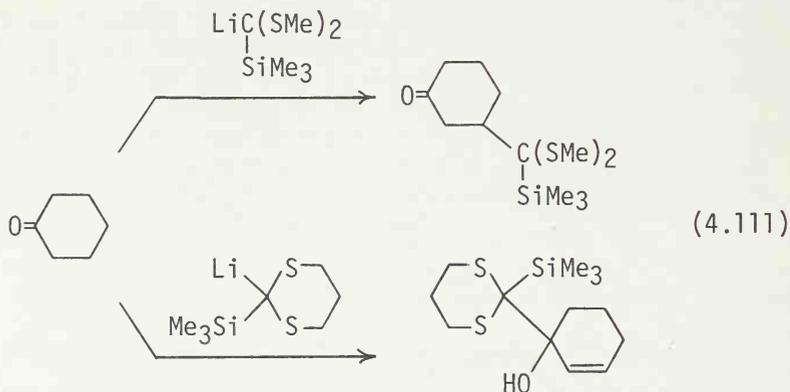
Scheme 4.2



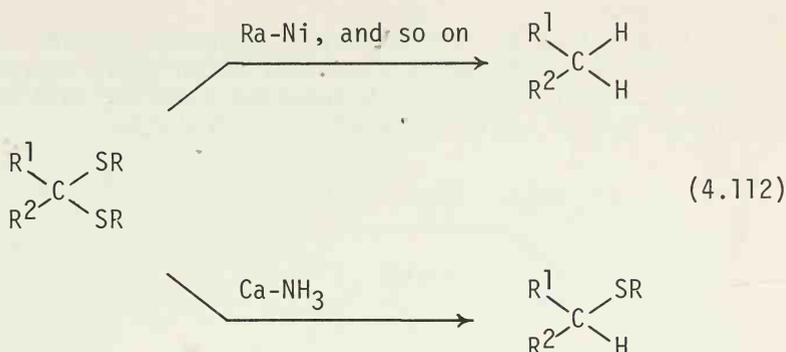
It should be noted that 2-lithiodithiane and its derivatives normally undergo only 1,2-addition reactions with α,β -unsaturated carbonyl compounds.

The dithiane ring is relatively stable and can withstand various conditions required for other reactions. This often represents an advantage as well as a disadvantage. Its conversion to the carbonyl group has presented a difficulty in some cases. Over the past several years, a number of methods for this transformation have been developed. The reagents used in these procedures include $\text{HgO}\cdot\text{BF}_3\cdot\text{OEt}_2$ (4.265), $\text{CuCl}_2\text{-CuO}$ -aq acetone (4.266), $\text{TiCl}_4\text{-HOAc-H}_2\text{O-CHCl}_3$ (4.267), $\text{Tl}(\text{OCCF}_3)_3$ (4.268), $\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6$ (4.269), chloramine T- $\text{H}_2\text{O-MeOH}$ (4.270), mesityl- SO_2ONH_2 (4.271), NCS and NBS (4.272), and various alkylating agents, such as MeI, MeOSO_2F , and Meerwein salts (4.273).

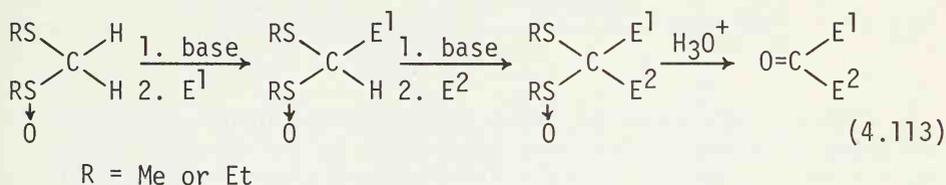
As shown in Table 4.13, a number of other cyclic and acyclic S,S-acetals have been suggested as dithiane substitutes. Relative advantages and disadvantages of these acyl anion equivalents are not very clear, however, because experimental data for comparison are usually not available. Lithiodithiolane is too unstable to be of practical use. One noteworthy advantage of using acyclic S,S-acetals is being able to achieve the 1,4-addition with α,β -unsaturated carbonyl compounds which tend to undergo the 1,2-addition reaction with the corresponding dithiane derivatives, as shown in eq. 4.111 (4.274).



Both cyclic and acyclic S,S-acetals can be totally desulfurized by Raney nickel (4.275), $\text{LiAlH}_4\text{-CuCl}_2\text{-ZnCl}_2$ (4.276), $\text{LiAlH}_4\text{-TiCl}_4$ (4.277), and hydrazine (4.278). On the other hand, treatment with calcium in liquid NH_3 converts S,S-acetals into sulfides; see eq. 4.112 (4.279).



Methyl methylthiomethyl sulfoxide and related S,S-acetal S-oxides. Methyl methylthiomethyl sulfoxide (MMTS) (4.213) and its ethyl homologue (4.214) have been developed as useful alternatives to dithiane and related S,S-acetals (eq. 4.113). Although the ethyl derivative is less readily available of the two, it is reported to be superior to MMTS in some reactions presumably due to the absence of competitive methyl hydrogen abstraction.

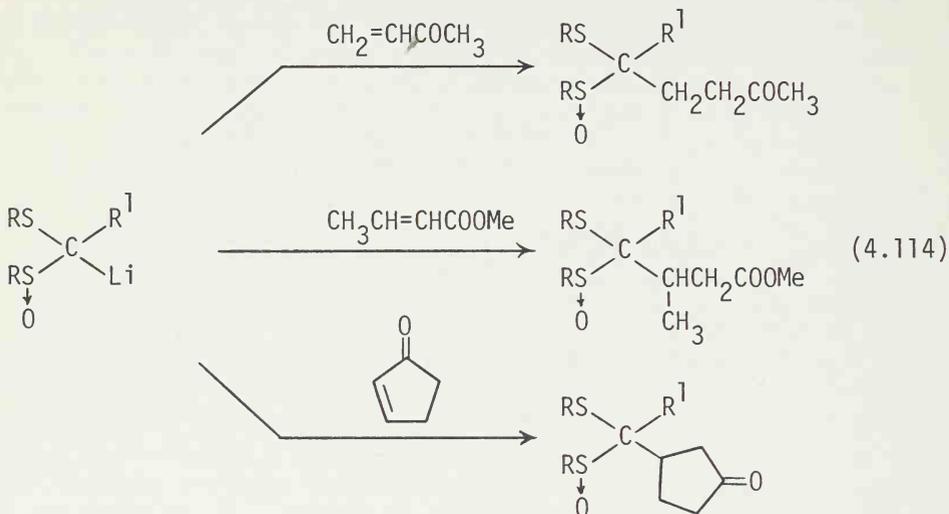


These S,S-acetal S-oxides are considerably more acidic than S,S-acetals. Consequently, generation of their metallated derivatives can be achieved with a variety of bases, such as *n*-BuLi, LDA, NaH, and KH.

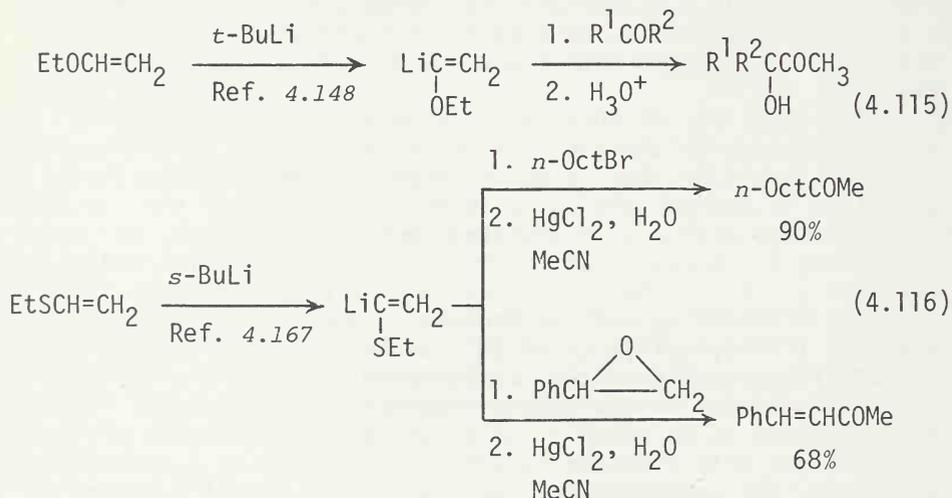
The reactions of these metallated species are generally quite analogous to those of lithiodithianes. The following differences should be clearly noted, however. Whereas metallated S,S-acetals in general are quite reluctant to undergo the 1,4-addition reaction with α,β -unsaturated carbonyl compounds, the corresponding S,S-acetal S-oxides readily undergo the 1,4-addition reaction (4.280). The 1,4/1,2 ratio of a given reaction, however, is affected by various factors. Thus it has been reported that the lithio derivative of MMTS undergoes predominantly the 1,2-addition reaction with cyclohexenone, whereas the 1,4-addition predominates in the case of cyclopentenone (4.280b). Another difference to be noted is that, whereas the reaction of lithiodithiane with cyanides is often complicated by α -hydrogen abstraction, the corresponding reaction of S,S-acetal S-oxides is

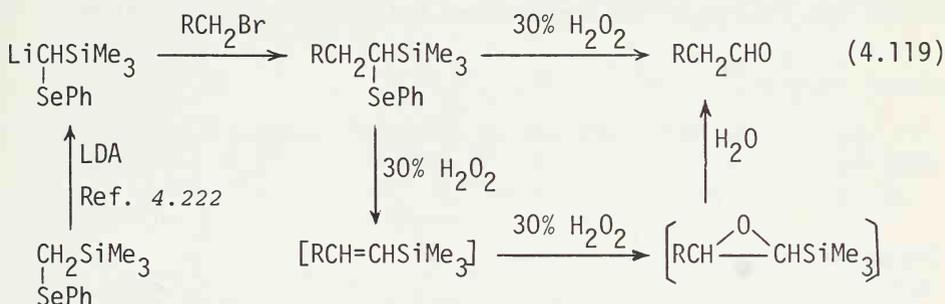
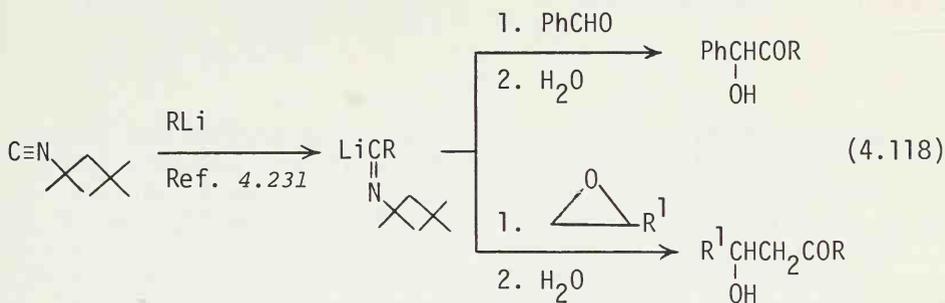
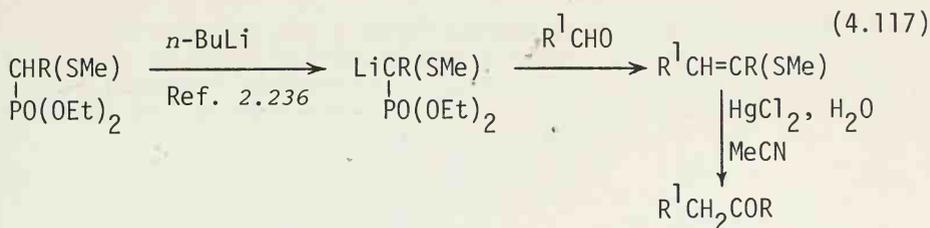
straightforward.

Since sulfoxides are chiral, *S,S*-acetal *S*-oxides are often obtained as diastereomeric mixtures, which could represent an inconvenience. Conversion of *S,S*-acetal *S*-oxides into carbonyl compounds can be achieved by acidic hydrolysis.



Others. As shown in Table 4.13, various other α -hetero-substituted organometallics have been shown to act as acyl anion equivalents. Several notable examples are shown in eqs. 4.115 to 4.119.

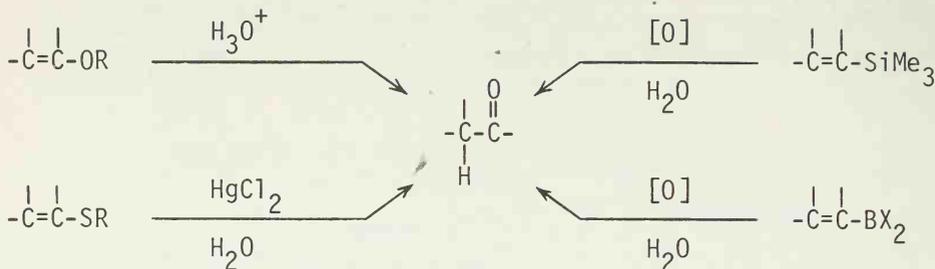




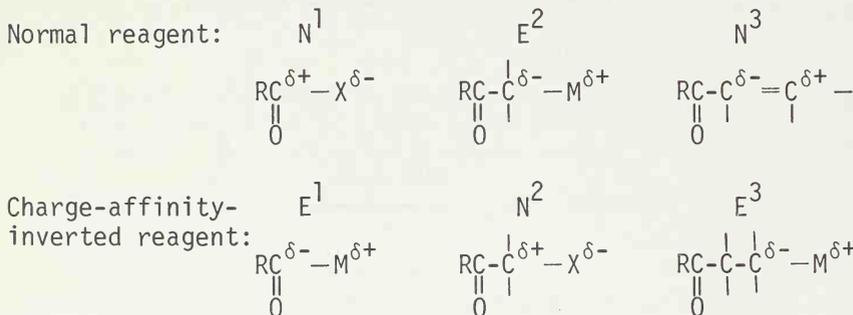
It is instructive to note that, except in eq. 4.118, hetero-substituted alkenes act as key intermediates, which are converted into the corresponding carbonyl compounds via oxidation and/or hydrolysis (Scheme 4.3). Similarly, alkenylboranes can be oxidized to give aldehydes and ketones (Sect. 5.2.3.2).

As mentioned earlier, it is often difficult to identify the most suitable masked carbonyl reagent for a given synthetic task. Nevertheless, various reagents discussed above seem to add considerable flexibility to the carbon-carbon bond formation via acyl anion equivalents.

Scheme 4.3

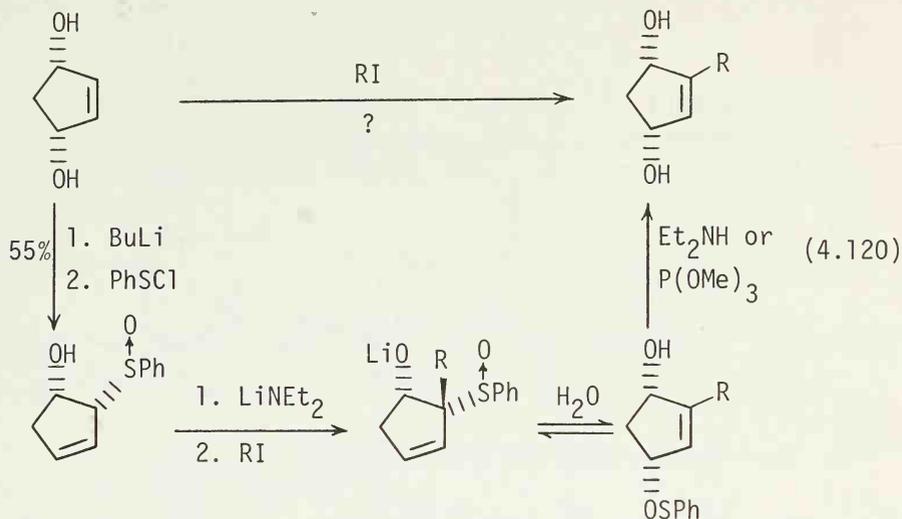


1,3 Charge Affinity Inversion Operations. Generation and use of acyl anion equivalents represent but one of many possible types of charge affinity inversion operations. To classify various types of normal and charge-affinity-inverted reagents, Seebach (4.257) has proposed the terms E^n and N^n to represent electron-donating and electron-accepting species, respectively, that have a reactive center on the n th carbon atom. Several examples of normal and charge-affinity-inverted reagents are shown below.



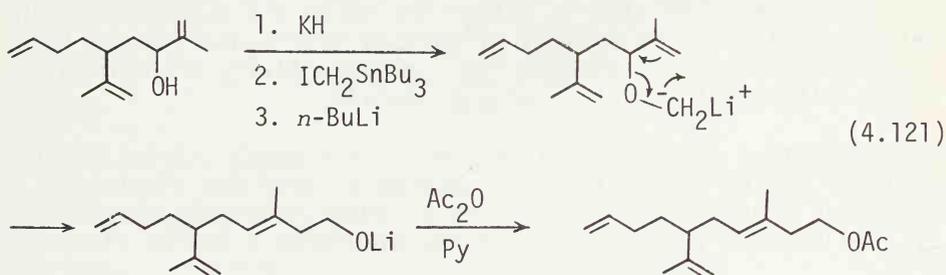
So far we have dealt only with E^1 reagents, that is, acyl anion equivalents. Generation of E^1 reagents and their use as N^1 substitutes, that is, $E^1 \rightarrow N^1$ operation, or any $E^n \rightleftharpoons N^n$ operation may be termed the 1,1 charge affinity inversion operation, as suggested by Evans (4.281). It is conceivable that a series of 1, n charge affinity inversion operations could be developed, where $n = 1, 2, 3$ and so on. At present, however, the 1,3-inversion operation appears to be the only inversion operation other than the much more common 1,1-inversion operation. In addition to the reviews by Seebach (4.256, 4.257) and Lever (4.258) cited above, a review by Evans (4.281) presents a lively discussion of the 1,3-inversion operation.

Alkylation on the alkenyl carbon atom of 2-cyclopenten-1,4-diol with an alkyl halide is not a normal synthetic operation. It can, however, be achieved via a 1,3-inversion operation, as shown in eq. 4.120 (4.183).

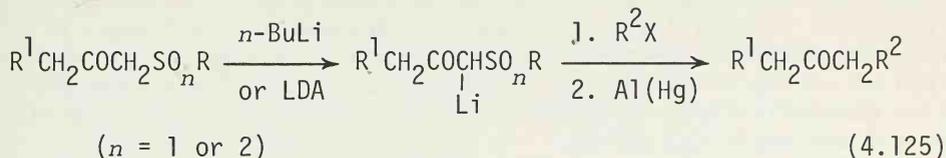


This principle has been applied to the synthesis of a number of γ -substituted allylic alcohols. It should be clearly noted that the 2,3-shift of allylic sulfoxides and sulfenates plays a crucial role in the sequence shown in eq. 4.120.

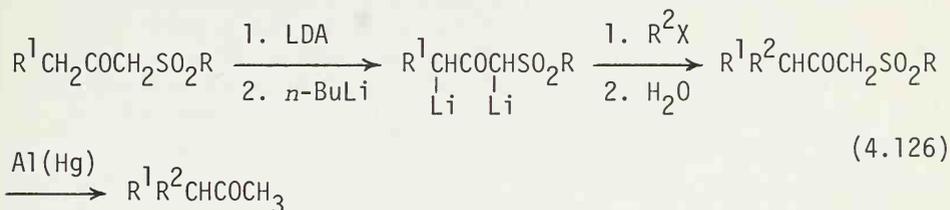
Other Carbon-Carbon Bond-Forming Reactions of α -Hetero-Substituted Organometallics Involving Sigmatropic Shifts. Other 2,3- and 3,3-shifts have been combined with the alkylation of α -oxy (4.282), α -thio (4.172, 4.175, 4.176), and α -seleno (4.220) organolithiums to develop stereoselective procedures for the synthesis of olefins.



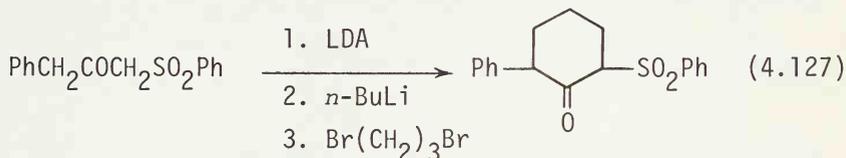
tive to the classic alkylation reaction of malonic and acetoacetic esters.



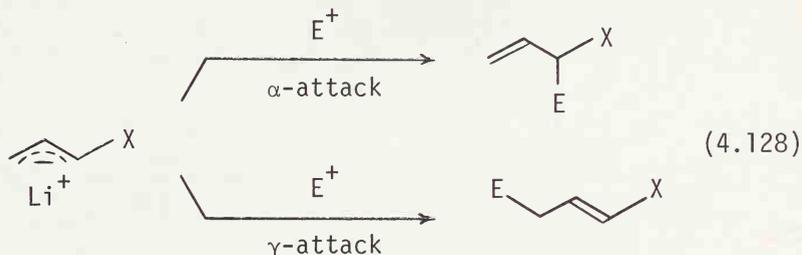
The corresponding dianions permit monoalkylation on the less acidic α -carbon atom (eq. 4.126).



It is also possible to dialkylate the dilithio derivatives, as shown in eq. 4.127 (4.283).

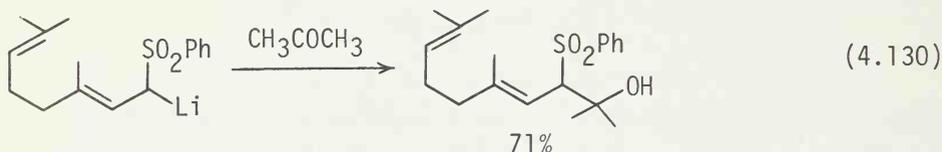
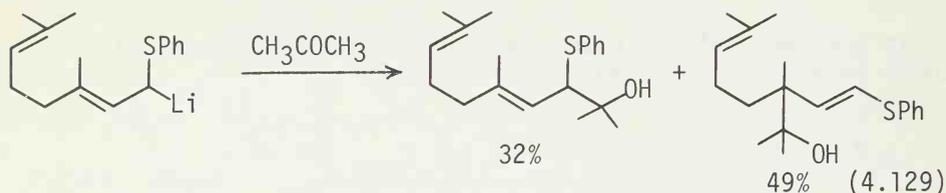


Regioselective Carbon-Carbon Bond Formation Involving Allylic Organoalkali Metals. Several extensive reviews on this subject are available (4.20, 4.257, 4.258, 4.281). As already indicated in the preceding section, α -hetero-substituted allyllithiums can undergo, in favorable cases, highly regioselective carbon-carbon bond formation (eq. 4.128).

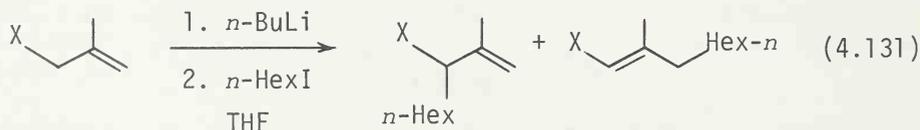


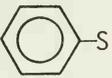
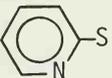
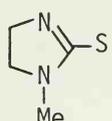
The α/γ ratio, however, is a function of a number of factors including the nature of X, and the nature of other substituents, conjugations, electrophiles, solvents, and additives. Unlike the alkylation of metallated β -carbonyl sulfoxides and sulfones, it is often difficult to attain a high regioselectivity in the reaction of α -hetero-substituted allylmetals. The following tentative generalizations concerning the α/γ ratio are presented here as a crude empirical guide.

(a) α -Hetero substituents. The heteroatom groups SR, SOR, SO₂R, SeR, and POX₂ tend to direct electrophilic attack at the α -position, whereas the OR and NR₂ groups favor attack at the γ -position. The α/γ ratio tends to increase in the order: SR < SOR < SO₂R. Thus whereas the lithium derivative of an allylic sulfide reacts with aldehydes and ketones at both α - and γ -positions, the corresponding sulfone tends to react exclusively at the α -position, for example, eqs. 4.129 and 4.130 (4.284).

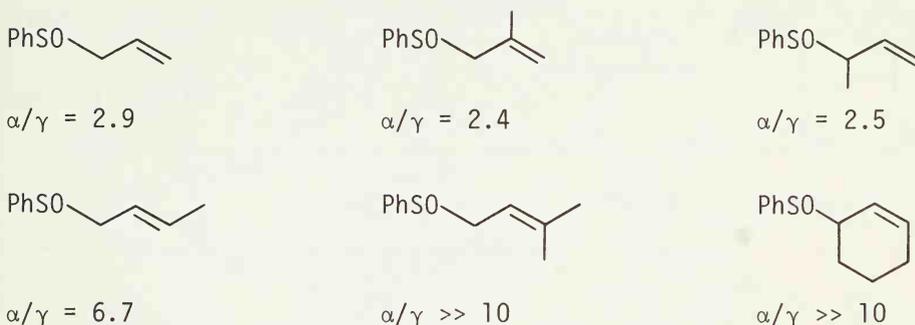


Replacement of the phenyl group of phenyl sulfides with nitrogen-containing heteroaromatic rings increases the α/γ ratio, presumably through chelation; see eq. 4.131 (4.281).

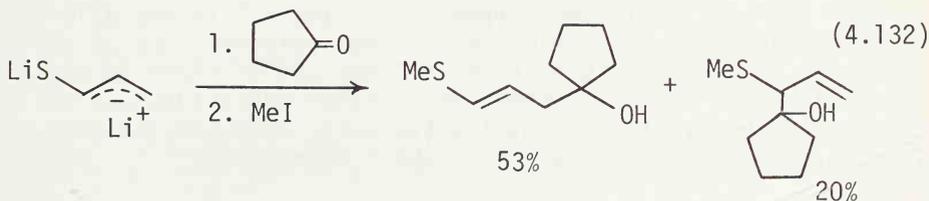


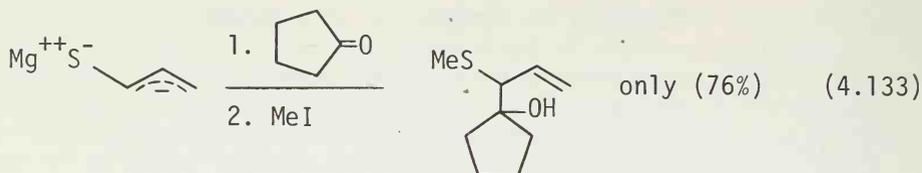
X	Yield (%)	α (%)	γ (%)
	84	75	25
	79	90	10
	86	92	8

(b) Substituents on allylic atoms. The α/γ ratio depends on the substitution pattern in the allylic moiety, as summarized below for the ethylation reaction of allylic sulfoxides (4.281).



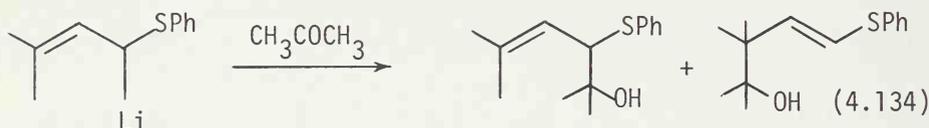
(c) Gegenions. The dilithio derivative of allylmercaptan reacts with electrophiles to give mixtures of α - and γ -products, with the latter predominating (eq. 4.132), whereas the magnesium derivative gives the α -products exclusively; see eq. 4.133 (4.257).





(d) Electrophiles. The α/γ ratio is often very much dependent on the nature of electrophiles. For example, whereas the alkylation of the lithium derivatives of allylic sulfides takes place predominantly at the α -position, for example, eq. 4.44, their reaction with carbonyl compounds tends to occur predominantly in the γ -position, for example, eq. 4.129.

(e) Solvents and additives. The α/γ ratio in the reaction of lithium derivatives of allylic sulfides with carbonyl compounds also depends on the solvent used as well as strongly coordinating additives, as exemplified by the results shown in eq. 4.134 (4.285).



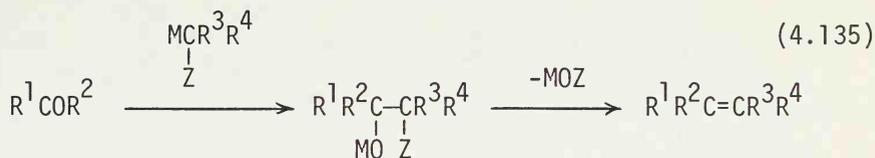
Solvent	Additive	α (%)	γ (%)
THF	-	25	75
THF	DABCO	0	100
THF	HMPA	40	60
THF	[2.2.2] cryptate	100	0

In summary, while the currently available data may allow us to make reasonable predictions as to the regiochemistry of the reactions of α -hetero-substituted allylmetals of Group IA and Group II metals with electrophiles, further investigations will be required before the practicing synthetic chemists can make extensive use of these reactions to their advantage.

4.3.3.3 Olefination Reactions Involving α -Hetero-Substituted Organometallics of Group IA and Group II Metals

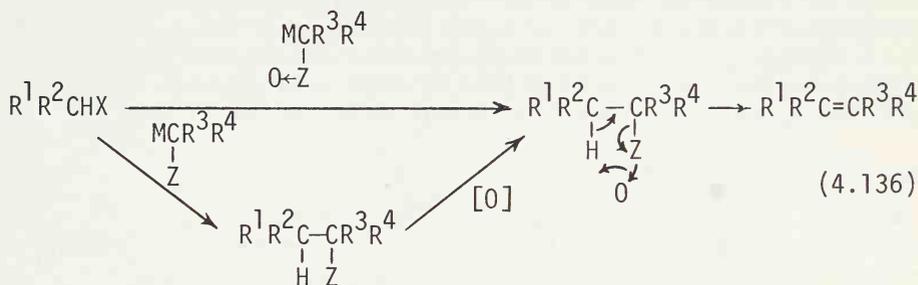
Some applications of α -hetero-substituted organolithiums to the synthesis of olefins via olefin interconversion are discussed in Sect. 4.3.3.1. In this section, applications of α -hetero-substituted organometallics to the synthesis of olefins via olefination are briefly discussed. A few synthetic strategies that have been exploited in the olefination of α -hetero-substituted organoalkali metals are shown below:

1. Carbonyl olefination reactions



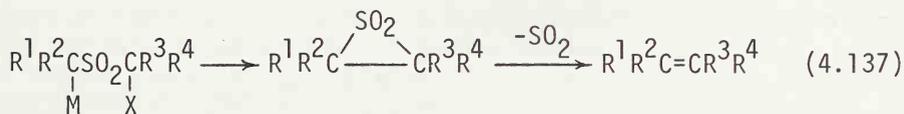
Z = P, Si, and S groups, M = alkali metals

2. Olefination via 2,3-shift reactions



Z = S and Se groups, M = alkali metals

3. Olefination via sulfur extrusion

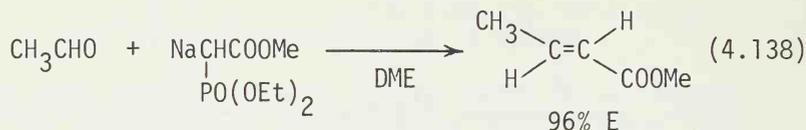


M = alkali metals

Carbonyl Olefination Reactions. Although the Wittig reaction is probably the most commonly used carbonyl olefination reaction, it

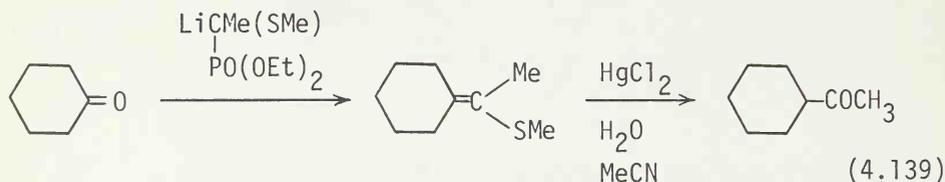
is not an organometallic reaction, and is therefore outside the scope of this book. The reader is referred to reviews by Maercker (4.286), Schlosser (4.287), and Johnson (4.288).

(a) The Wadsworth-Emmons reaction. The carbonyl olefination reaction of α -metallated phosphonates, called the Wadsworth-Emmons reaction, is a useful modification of the Wittig reaction. Some representative examples are summarized in Table 4.11. In cases where the carbonyl compound is an aldehyde, the Wadsworth-Emmons reaction often, but not always, leads to the formation of the (E)-isomer in a highly stereoselective manner (~95% selectivity), as shown in eq. 4.138 (4.233).



The stereoselectivity of the Wadsworth-Emmons reaction appears to be generally higher than that of the corresponding Wittig reaction. The reaction of α -metallated phosphonates with ketones, however, in general, is not stereoselective. Even in the olefination of aldehydes, the use of sterically hindered phosphonates produces mixtures of (E)- and (Z)-isomers (4.233d).

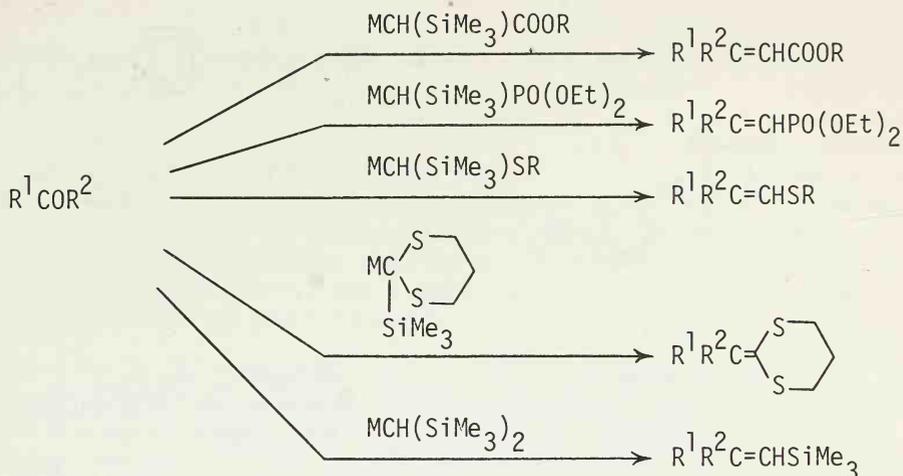
Introduction of additional hetero substituents in the phosphonate ester can provide unique synthetic procedures as exemplified by the transformation shown in eq. 4.139 (4.289).



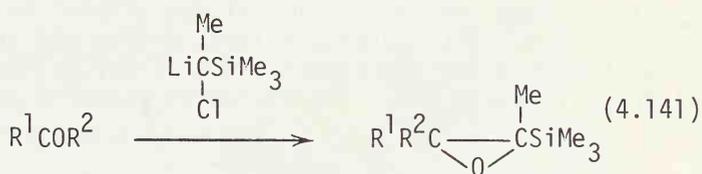
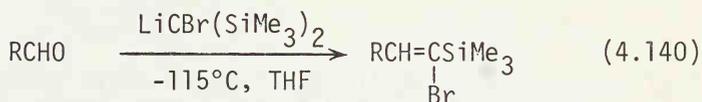
(b) The Peterson reaction. The reaction of α -silylorganoalkali metals with carbonyl compounds, known as the Peterson reaction, provides an alternate method for the carbonyl olefination. A variety of α -silylorganoalkali metals, such as those summarized in Table 4.12, undergo this olefination reaction. Several representative examples are shown in Scheme 4.4.

Unlike the Wadsworth-Emmons reaction, the Peterson reaction is seldom highly stereoselective. It does, however, provide a convenient route to certain hetero-substituted olefins, as shown

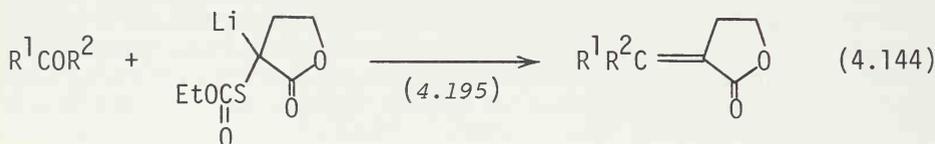
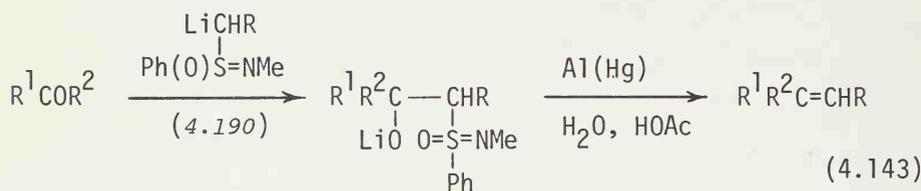
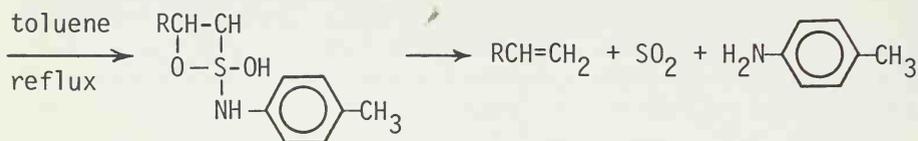
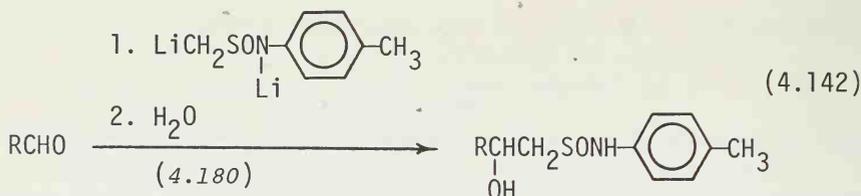
Scheme 4.4



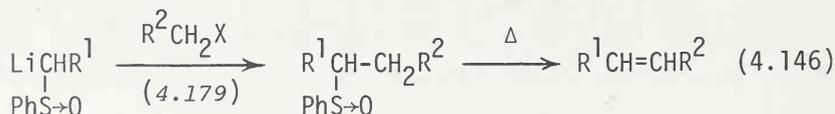
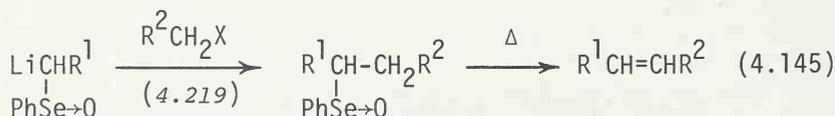
in Scheme 4.4. It is important to notice that the olefin-forming ability of a trialkylsilyl group is greater than that of a phosphonate group. It should also be noted that the reaction of α -halo- α -silylorganometals with carbonyl compounds can form either olefins or epoxides; see eqs. 4.140, 4.141 (4.139, 4.138).

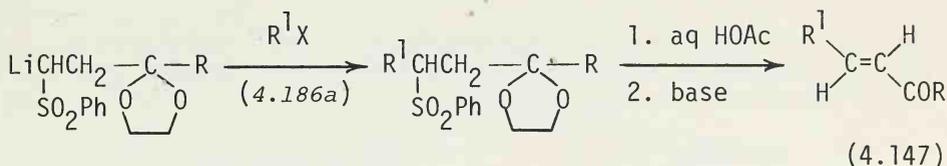
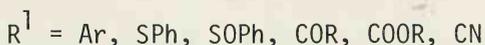


(c) Miscellaneous carbonyl olefination reactions. Certain organoalkali metals containing α -sulfur substituents can undergo carbonyl olefination reactions similar to the Wadsworth-Emmons and Peterson reactions. A few representative examples follow.



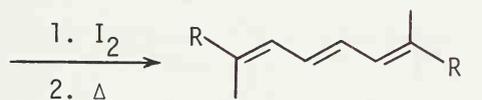
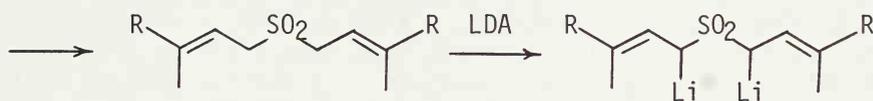
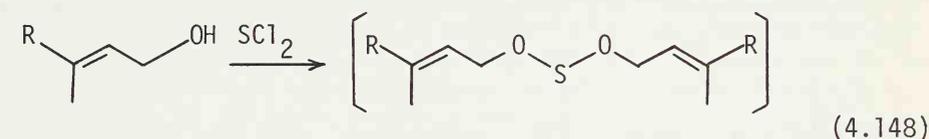
Olefination via 2,3-Shift Reactions. Alkyl sulfoxides and selenoxides undergo a thermal 2,3-sigmatropic shift reaction to form olefins. Thus the combination of the alkylation of α -sulfur- or α -selenium-substituted organoalkali metals and the 2,3-shift provides a method for the conversion of alkyl halides into olefins, as shown in eq. 4.136. The following examples are representative.



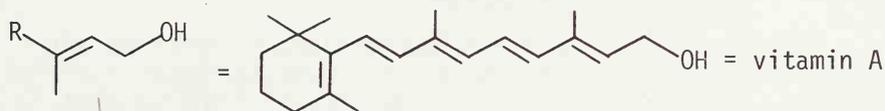


The formation of α,β -unsaturated carbonyl compounds and related conjugated olefins is stereoselective, producing the more stable (E)-isomers. For further details of olefination via organoseleniums and organosulfurs, the reader is referred to reviews by Clive (4.290) and Trost (4.291), respectively.

Olefination via Sulfur Extrusion. Although more limited than the other olefination reactions of α -hetero-substituted organometallics discussed above, the Ramberg-Bäcklund reaction (4.292), the sulfur analogue of the Favorskii rearrangement, provides a unique route to olefins (eq. 4.137).

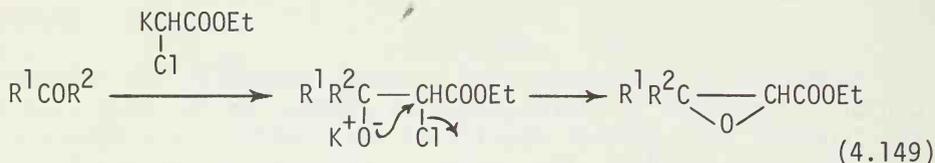


all-*trans*- β -carotene

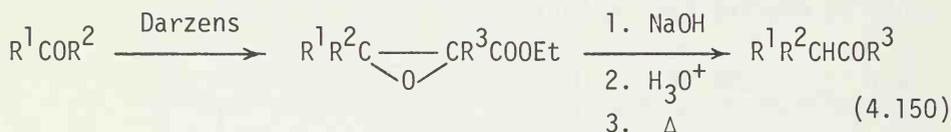


4.3.3.4 Epoxidation Reactions Involving α -Hetero-Substituted Organometallics of Group IA and Group II Metals

The Darzens glycidic ester condensation (4.294) represents a classic example of epoxidation of aldehydes and ketones with α -haloorganometallics (eq. 4.149).

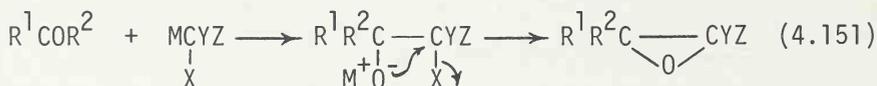


Although no detailed discussion of the Darzens reaction is intended here, it should be pointed out that, in many cases, the reaction produces (E)-isomers stereoselectively. The main synthetic use of the Darzens reaction lies in the carbonyl interconversion shown in eq. 4.150.



Unfortunately, however, the conversion of glycidic esters into carbonyl compounds is usually a low-yield process.

As summarized in Table 4.6, a wide variety of α -haloorganometallics containing alkali metals have been shown to undergo epoxidation reactions which presumably are closely related to the Darzens reaction. These reactions are represented by eq. 4.151.



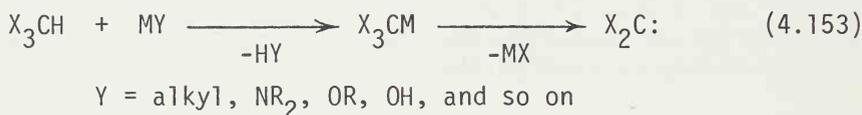
X = Cl, Br, or I; Y, Z = H, alkyl, aryl;

CN, SR, SOR; SO₂R, SiR₃, and so on

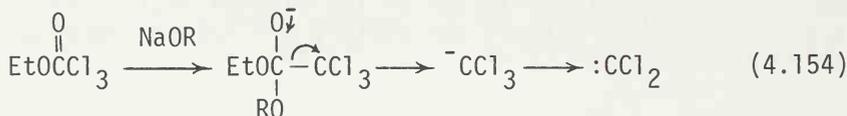
Related to these epoxidation reactions is the reaction of carbonyl compounds with either sulfonium or sulfoxonium ylides (4.295). Some recent results (4.161, 4.191) indicate that it is often more advantageous to use the corresponding sulfur-containing organometallics and generate the required sulfur betain intermediates via alkylation, as shown in eq. 4.152, especially in

benes generated from α -heteroorganometallics. As originally proposed by Skell (4.296), the cyclopropanation reaction of singlet carbenes is believed to be a concerted process and should therefore be stereospecific, whereas the corresponding reaction of triplet carbenes must be a stepwise, nonstereospecific process. In this section, some carbene or carbenoid reactions of α -hetero-substituted organometallics of Group IA and Group II metals is discussed briefly. The reaction of α -haloorganomercuries is discussed in Sect. 7.3.2.2, and the chemistry of transition metal-carbene complexes is discussed in Chap. 12.

Halocarbenes. Haloforms are sufficiently acidic so that their treatment with a variety of bases can produce the corresponding dihalocarbenes; see eq. 4.153 (4.119, 4.123).

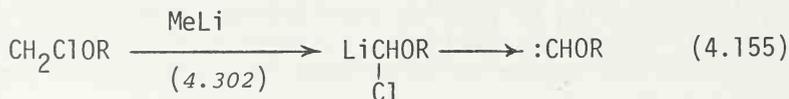


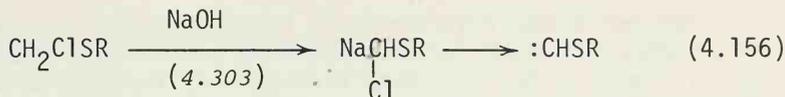
In addition to simple haloforms in which all three halogen atoms are the same, various "mixed" haloforms, such as CHFI₂ (4.297) and CHClBr₂ (4.298), can also serve as carbene precursors. The carbene products generated from mixed haloforms can be predicted on the basis of the relative leaving ability of halogens, that is, I > Br > Cl > F. Alternatively, trihaloacetic acids and their esters can be treated with bases to produce carbenes, as shown in eq. 4.154 (4.299).



Generation of monohalocarbenes from dihalomethanes requires highly basic reagents, such as organolithiums (4.300) and alkali metal amides, such as NaN(SiMe₃)₂ (4.301).

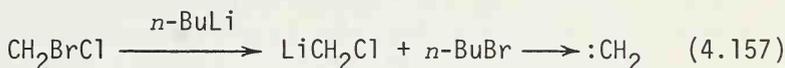
Other Hetero-Substituted Carbenes. Various hetero-substituted carbenes can be generated by treating appropriate α -hetero-substituted organic halides and related derivatives with strong bases, as shown in eqs. 4.155 and 4.156.





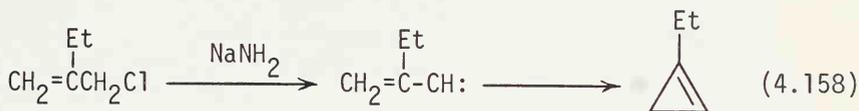
Methylene and Its Derivatives Substituted with Carbon Groups.

Although methyl halides have not successfully been converted into methylene by treatment with bases, certain dihalomethanes can be treated with alkylolithiums at low temperatures to form methylene via metal-halogen exchange, as shown in eq. 4.157 (4.114).

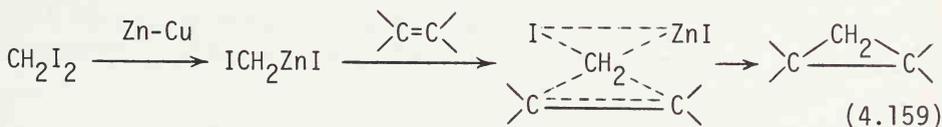


In general, the metal-halogen exchange reaction of polyhalogenated compounds, especially those containing iodine and bromine, provides a useful alternative to the metal-hydrogen exchange route (4.300).

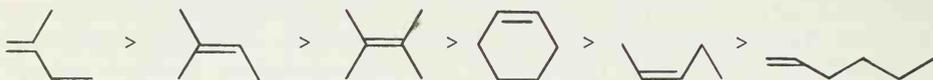
Higher alkyl halides containing β -hydrogen atoms preferentially undergo β -elimination when treated with strong bases. On the other hand, benzylic halides can be converted into benzylic carbenes, which can undergo the expected cyclopropanation reaction (4.304). The corresponding reaction of allylic halides leads to the formation of cyclopropenes via intramolecular cyclopropanation, as shown in eq. 4.158 (4.305).



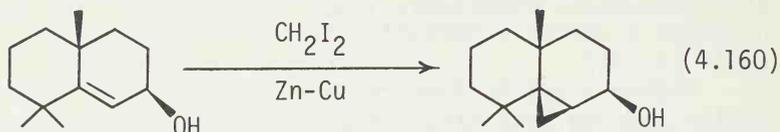
The Simmons-Smith Reaction. The reaction of the organozinc reagent prepared from methylene iodide and Zn-Cu couple with olefins, known as the Simmons-Smith reaction, has proved to be a convenient method for the synthesis of cyclopropanes (4.127, 4.306). The active species is believed to be iodomethylzinc iodide rather than free methylene. The following concerted mechanistic scheme has been proposed (4.306, 4.307), and is consistent with the observed data.



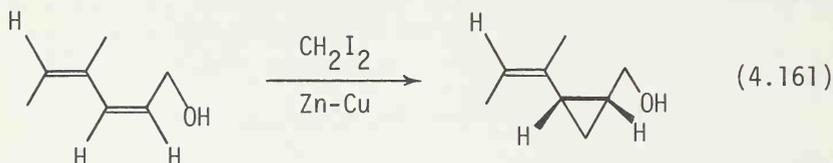
Thus the reaction is first-order in both olefin and ICH_2ZnI . Although electron-donating substituents of olefins, such as alkyl groups, tend to facilitate this reaction, there is a delicate balance between electronic and steric effects, as reflected in the following reactivity order (4.306).



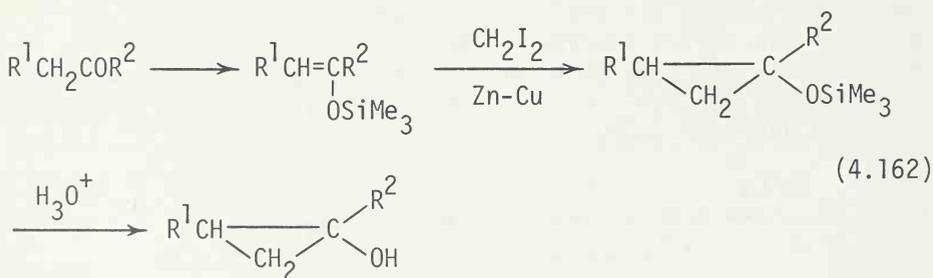
In general, attack by the Simmons-Smith reagents from the less hindered side of the double bond is preferred. Proximal oxy groups, such as OH and COOR, however, strongly favor attacking on the cis side of the oxy substituents, as shown in eq. 4.160 (4.308).



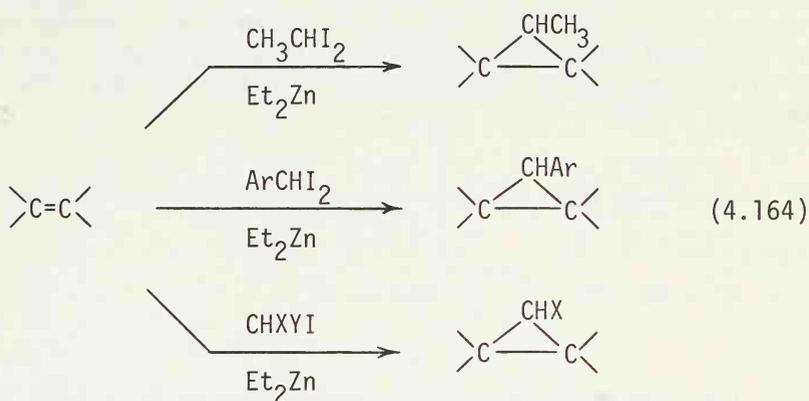
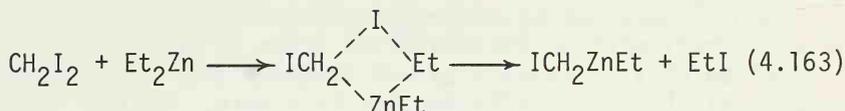
Another synthetically useful as well as mechanistically revealing feature of the reaction is that it proceeds with retention of the configuration of olefins, as shown in eq. 4.161 (4.309).



The reaction of the Simmons-Smith reagent with silyl enol ethers provides a convenient route to cyclopropanols; see eq. 4.162 and Sect. 6.4.2.2 (4.310).



The Furukawa Modification of the Simmons-Smith Reaction. An important modification of the Simmons-Smith reaction has been reported by Furukawa (4.311). In this modification, CH_2I_2 is treated with dialkylzinc, such as Et_2Zn , to generate the iodomethylzinc reagent via metal-halogen exchange. Unlike the generation of the Simmons-Smith reagent, this reaction is homogeneous and proceeds readily under mild conditions, thereby preventing various difficulties encountered in the original Simmons-Smith reaction.

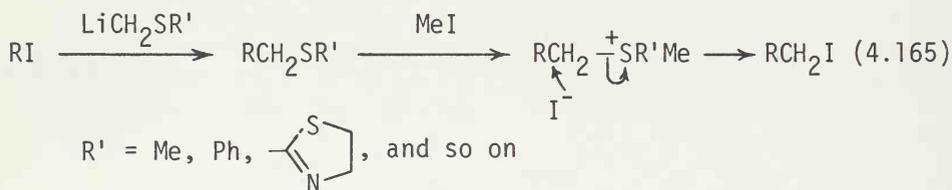


X, Y = F, Cl, Br, or I

As indicated in eq. 4.164, the Furukawa procedure appears to be much more general than the Simmons-Smith reaction. For example, whereas the Simmons-Smith reaction is not readily adaptable to alkylidene transfer, in many cases the modified procedure is readily applicable to this type of transformation. Cationically polymerizable olefins, such as vinyl ethers, are generally not very suitable for use in the Simmons-Smith reaction. On the other hand, the Furukawa reagents can react smoothly with such olefins. It is important to note that the modified procedure seems to retain essentially all advantageous features, such as stereospecificity, of the original procedure.

4.3.3.6 Miscellaneous Synthetic Applications of α -Hetero-Substituted Organometallics of Group IA and Group II Metals

Although the great majority of synthetic applications of α -hetero-substituted organometallics of Group IA and Group II metals are represented by the reactions discussed in the preceding sections, their applications to organic synthesis are by no means limited to those discussed above. The primary products in their reactions with carbon electrophiles (Scheme 4.1) and nucleophiles, such as olefins, can be further transformed into a myriad of organic compounds by taking advantage of the presence of α -hetero substituents. The synthetic scope of such transformations is limited only by creativity and imagination. A systematic discussion of this subject is not possible here. Only a few specific examples are discussed merely to indicate their synthetic potential yet to be fully explored. The reaction of alkyl halides, such as RI, with α -thiomethylithium derivatives followed by treatment with an appropriate alkylating agent, such as MeI, permits a one-carbon homologation of alkyl halides; see eq. 4.165 (4.160, 4.169).



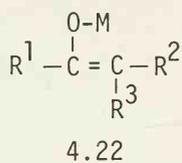
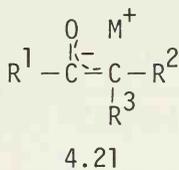
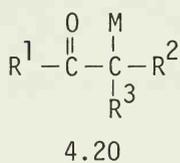
One inspiring example of imaginative explorations in this area is that of Trost (4.312). Taking advantage of the presence of an α -thio substituent as well as of the strained cyclopropyl ring, the products of the reaction of α -thiophenoxycyclopropyl-lithium (4.19) with carbonyl compounds have been converted into a variety of organic compounds, as exemplified by Scheme 4.5.

4.3.4 Carbon-Carbon Bond Formation via Alkali and Alkaline Earth Metal Enolates

4.3.4.1 General Considerations

Until recently, the chemistry of carbonyl compounds had dominated the carbon-carbon bond formation via polar reactions, and metal enolates had been major sources of carbanionic species. Although

Structure. Although some β -carbonyl organometallics represented by 4.20 containing relatively electronegative metals, such as Hg, Si, Ge, and Sn (4.319), are known, structure 4.20 appears to be unimportant in metal enolates containing relatively electropositive metals, such as Li, Na, K, and Mg.

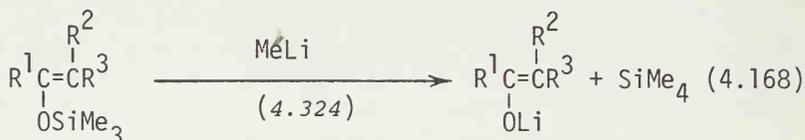
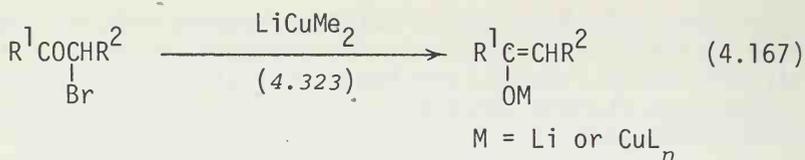


If the ionicity of the bonds to the metal atoms of metal enolates were very high, ionic structure 4.21 would be the most accurate representation of the monomer form of metal enolates. In such cases, the question of the M-O bonds versus the M-C bonds is rather meaningless. In reality, however, spectroscopic studies of certain lithium and sodium enolates (4.320, 4.321) suggest that, at least in these cases, structure 4.22 is most consistent with the available data. Thus, for example, the lithium enolate of phenylacetone exhibits a pair of strong IR absorptions in the 1550-1585 cm^{-1} region (4.320). Likewise, the ^1H NMR spectrum of lithioisobutyrophenone indicates two distinct methyl signals (4.321).

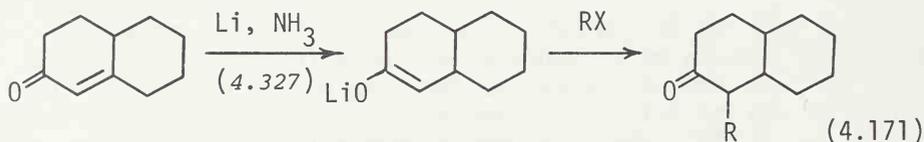
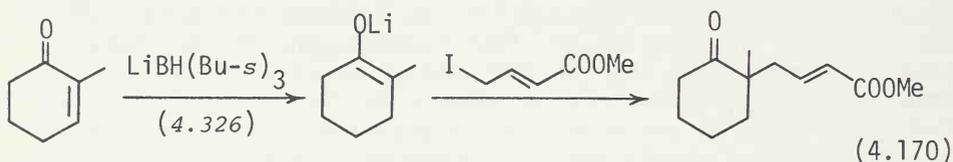
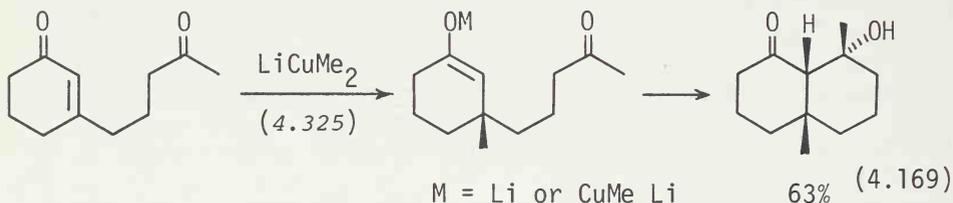
Another question of fundamental significance is that which concerns the degree of aggregation, as discussed in Sect. 4.1. The degree of aggregation of lithioisobutyrophenone has been studied by measuring the ^{13}C NMR relaxation times (4.322). The results indicate that it is tetrameric in THF, dioxane, and tetrahydropyran. In our subsequent discussion of metal enolates, in most cases we simply adopt the monomeric representation 4.22 for metal enolates regardless of their exact structures.

Preparation. By far the most important method for preparing metal enolates is metal-hydrogen exchange (Method V), although other methods commonly used for the preparation of "simple" organolithiums and Grignard reagents, such as oxidative metallation (e.g., eq. 4.166), metal-halogen exchange (e.g., eq. 4.167), and transmetallation (e.g., eq. 4.168), have also been used on occasion.

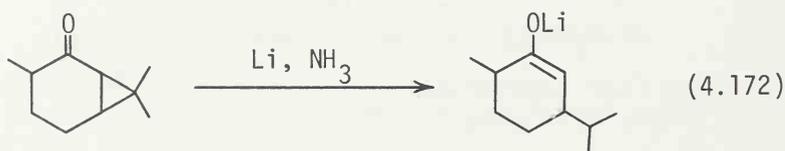




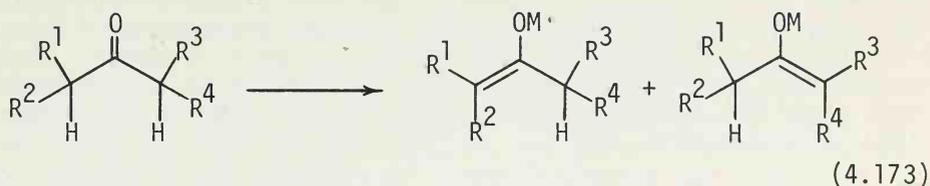
In addition to these methods, the conjugate addition of either organometallics (e.g., eq. 4.169) or metal hydrides (e.g., eq. 4.170) and the dissolving metal reduction of α,β -unsaturated carbonyl compounds (e.g., eq. 4.171) have provided regioselective routes to enolates.



Dissolving metal reduction is also applicable to the generation of enolates from cyclopropyl ketones; see eq. 4.172 (4.328).



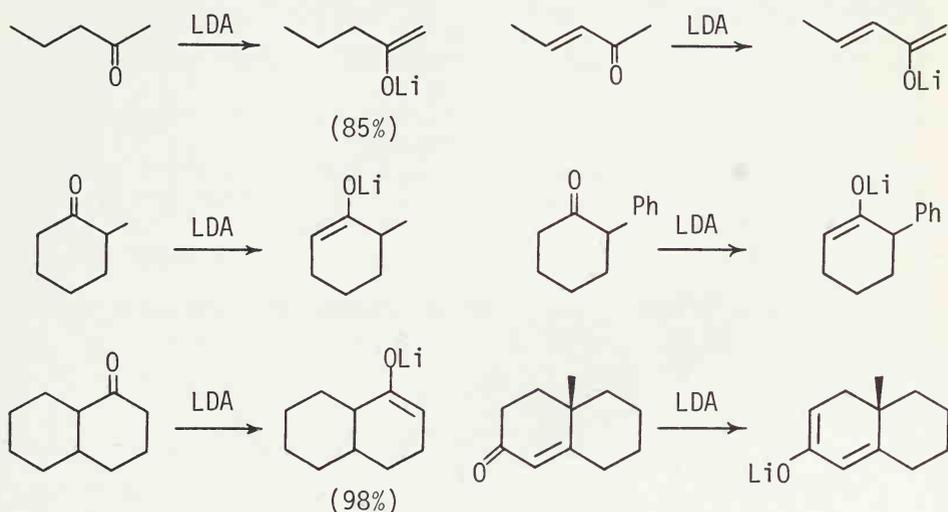
In the preparation of metal enolates via metal-hydrogen exchange, unsymmetrical ketones having both α - and α' -hydrogen atoms can give two regioisomeric enolates (eq. 4.173).



It is, of course, very desirable to be able to generate regioselectively either one of these two regioisomers.

Recent developments of nonnucleophilic but highly basic reagents, such as $\text{LiN}(\text{Pr-}i)_2$ (LDA), $\text{LiNPr-}i(\text{Hex-}o)$ (LICA), $\text{LiN}(\text{SiMe}_3)_2$, and $\text{KN}(\text{SiMe}_3)_2$, have made it possible to generate regioselectively "kinetic" enolates at low temperatures, -78°C , for example, in aprotic solvents, such as THF. Under these conditions, the least hindered hydrogen atom is abstracted, as shown in the following examples.

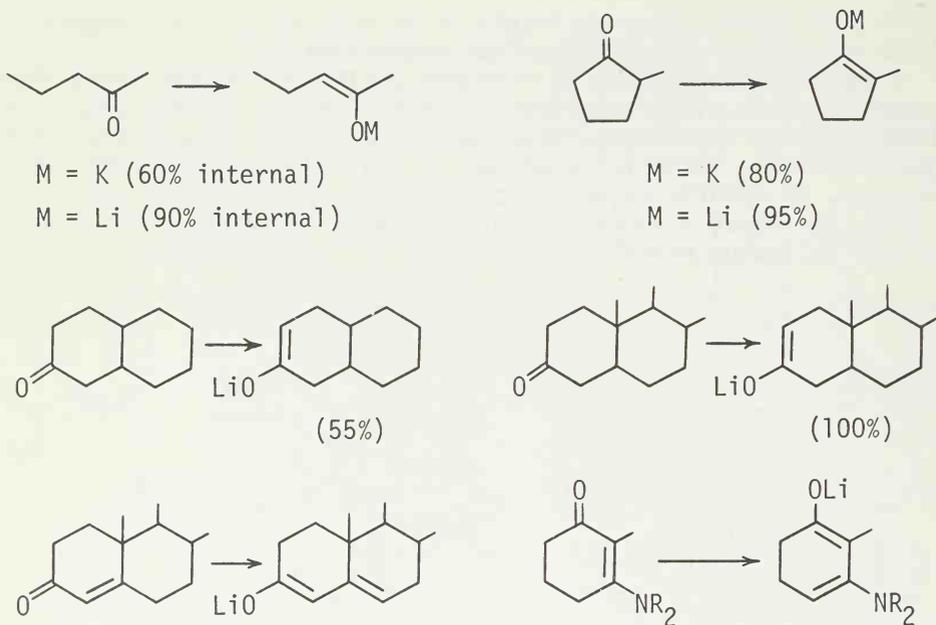
Scheme 4.7



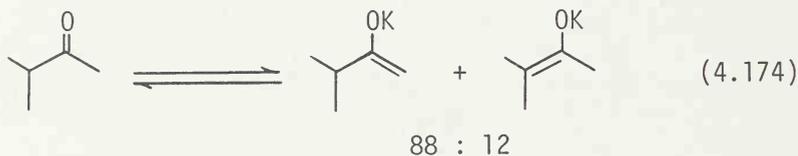
Ketones must be added slowly to a solution of a base to minimize the amount of free ketones that can act as proton donors capable of inducing undesirable scrambling.

In most cases, "kinetic" and "thermodynamic" enolates are different. Equilibration of enolates, which is strongly catalyzed by proton donors including the ketones used for the generation of enolates, usually leads to mixtures of two or more regioisomers in which "thermodynamic" enolates predominate. This is usually accomplished by generating enolates at or above room temperature in protic solvents. The equilibrium is dependent on both reagents and temperature. Some typical results are summarized in Scheme 4.8.

Scheme 4.8



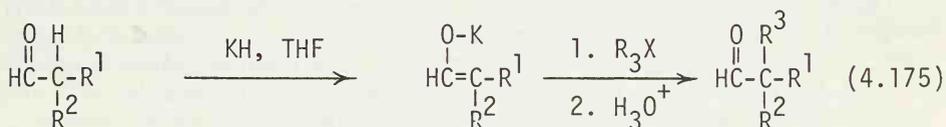
In some cases, "kinetic" and "thermodynamic" enolates are identical, as shown in eq. 4.174.



Although less general and less convenient, the other methods of generating enolates discussed above are regioselective. Therefore, under nonequilibrating conditions, regiochemically pure enolates can be generated.

Even in cases where no regiochemical problem exists, the extent of enolate formation is a matter of serious concern. Before the advent of strong nonnucleophilic bases, the synthetic organic chemist often dealt with enolates formed as equilibrium mixtures containing both the starting carbonyl compounds and their enolates. While the use of such equilibrium mixtures may be advantageous in some cases, they present a serious problem of self-condensation. Here again, however, the use of strong nonnucleophilic bases, such as LDA and LICA, has solved many problems associated with the enolates of carboxylic acids and their esters by permitting complete metal enolate formation (4.329).

An important addition to the list of strongly basic but non-nucleophilic bases is KH (4.330). Using KH as a base, not only ketones (4.330) but aldehydes; see eq. 4.175 (4.331), can be converted into enolates without the complication due to self-aldolization. On the other hand, esters cannot be converted into enolates with KH, since the Claisen condensation is highly competitive (4.332).

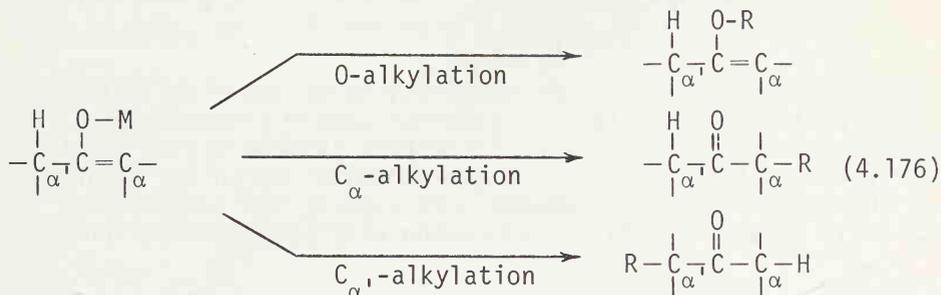


4.3.4.2 Alkylation of Metal Enolates

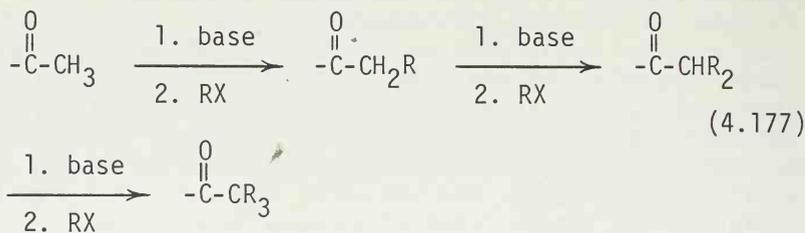
The alkylation of metal enolates has been reviewed by many authors (4.316 to 4.318). Although the reaction has been widely used, it has also been plagued with several difficulties, such as those listed below:

1. Regiochemistry,

- 1a. C-alkylation versus O-alkylation,
- 1b. α -Alkylation versus α' -alkylation,



2. Mono- versus poly-alkylation,

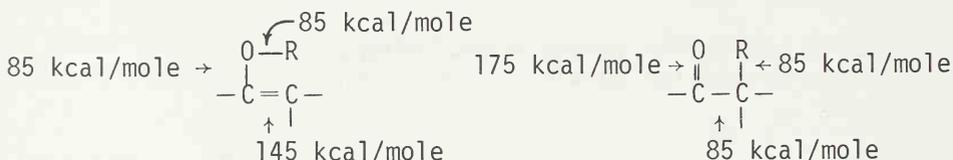


3. Stereochemistry,

4. Chemoselectivity,

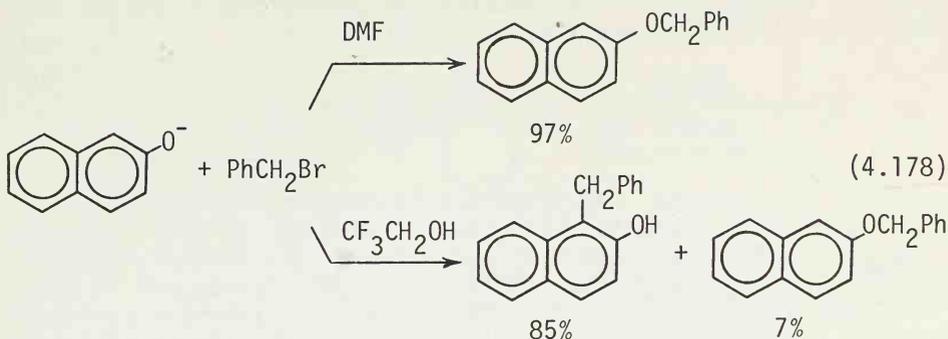
5. Use of alkenyl, aryl, alkynyl, and hindered alkyl halides.

C-Alkylation Versus O-Alkylation. The C-/O-alkylation ratio is a function of various factors, of which the following appear to be some of the most significant. Firstly, as already pointed out in Sect. 1.6, the oxygen and α -carbon atoms represent the "hard" and "soft" ends of enolates. Thus the C-/O-alkylation ratio increases as the softness of the alkylating agent increases. For example, the C-/O-alkylation ratio increases in the order: ROTs < RCl < RBr < RI. Likewise the C-/O-alkylation ratio generally increases, as the ionicity of the metal-to-enolate bond decreases: $\text{N}^+\text{R}_4 < \text{K}^+ < \text{Na}^+ < \text{Li}^+$. Secondly if one compares the bond energies of C- and O-alkylation products, it is evident that, in the absence of any special effects, the C-alkylated products are thermodynamically more stable than the O-alkylated products.



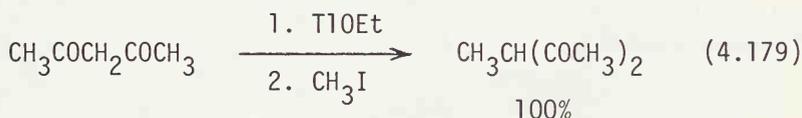
If the difference in product stability is strongly reflected in the transition state, the C-alkylation should predominate. Thirdly, solvents play an important role in determining the C-/O-alkylation ratio. If there is strong solvation in the vicinity of the oxygen atom and a weaker solvation at the carbon atom, relatively greater reactivity at carbon will be observed. One of

the most dramatic manifestations of the solvent effects in enolate alkylation is shown in eq. 4.178 (4.333).



Polar aprotic solvents, such as DMF and DMSO, effectively solvate cations but not anions. The usual mode of phenolate alkylation involves attack at the oxygen site, and that is what we find. In $\text{CF}_3\text{CH}_2\text{OH}$ the oxygen end of the phenolate is strongly solvated through hydrogen bonding. This disfavors O-alkylation.

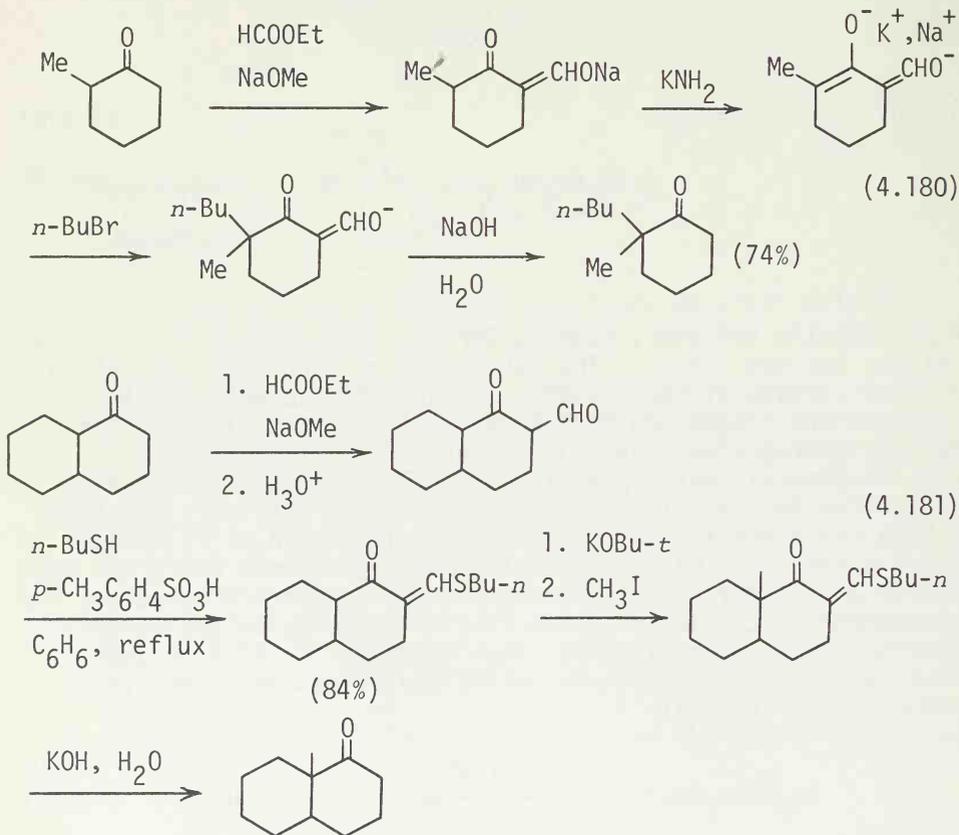
In general, metal phenolates tend to undergo O-alkylation in preference to C-alkylation. It is generally difficult to attain a high C-/O-alkylation ratio. In the alkylation of 1,3-dicarbonyl compounds, the C- and O-alkylation processes are often competitive. In most cases, however, their alkylation reactions can be steered in the desired direction by properly selecting metals, leaving groups, and solvents. For example, if TlOEt is used as a base, an exclusive C-methylation of acetylacetone takes place; see eq. 4.179 (4.334).



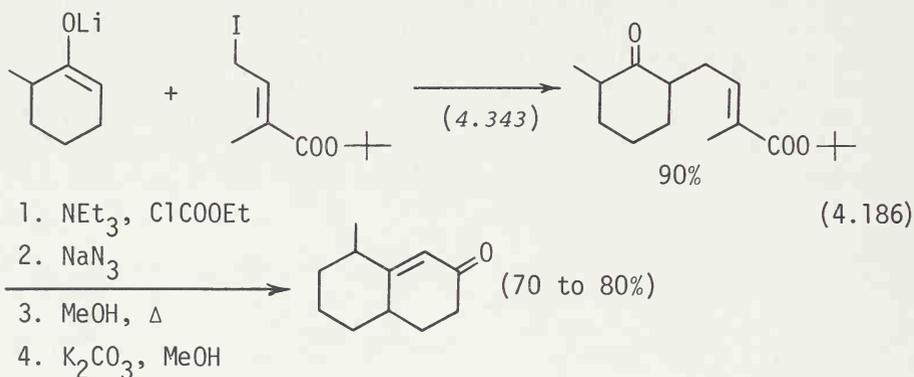
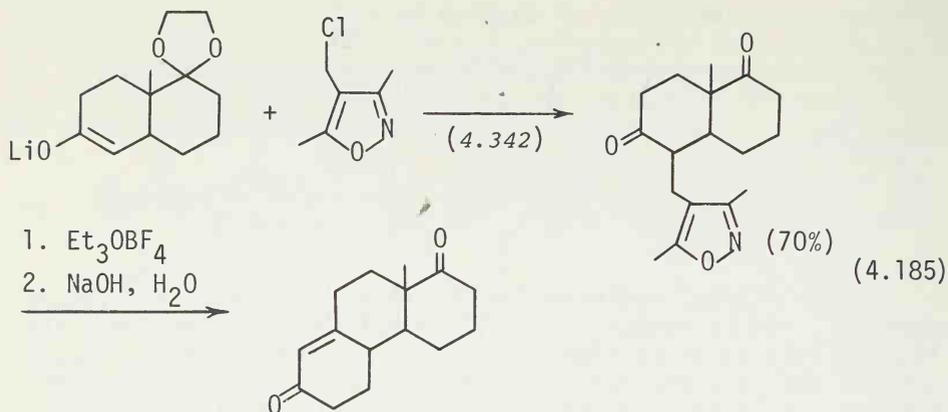
Finally, O-alkylation is usually not competitive in the alkylation of mono carbonyl compounds.

C_α -Alkylation Versus $C_{\alpha'}$ -Alkylation and Mono-alkylation Versus Poly-alkylation. One of the most commonly encountered difficulties in the alkylation of ketones is the formation of mixtures of regioisomers as well as of mono- and poly-alkylated products. Until recently, this problem had been solved mainly by some indirect methods including (1) malonic ester and acetoacetic ester

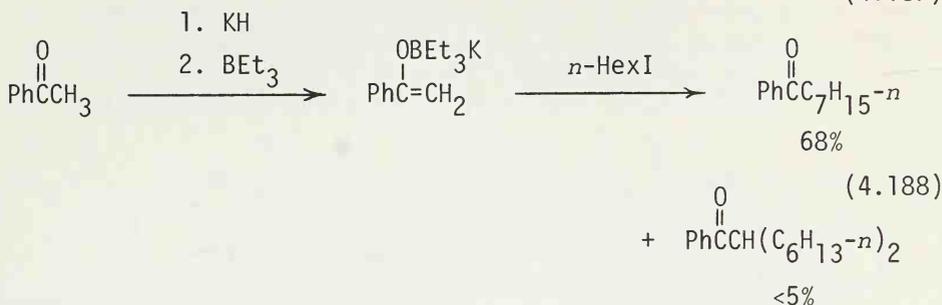
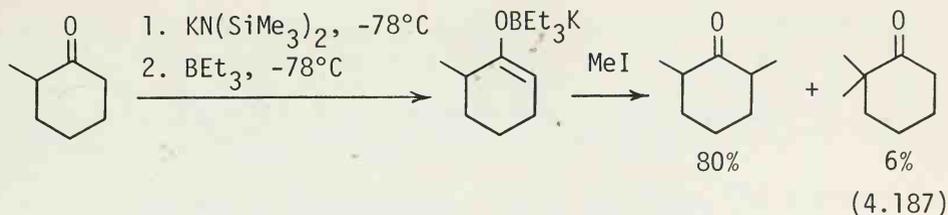
syntheses (4.335) and related methods for alkylation, for example, eq. 4.180 (4.336), (2) ketone syntheses via β -ketosulfones and β -ketosulfoxides discussed in Sect. 4.3.3.2, and (3) α -alkylation of ketones involving blocking and unblocking of one of the two α -positions, for example, eq. 4.181 (4.337).



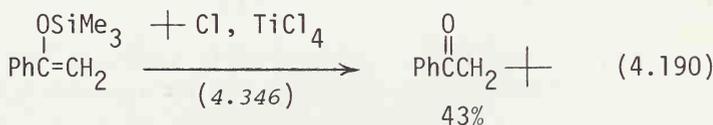
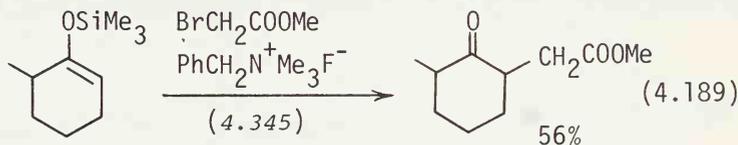
While these multistep methods are generally tedious and are being replaced gradually by simpler methods, such as those discussed later, some of these conventional methods are still valuable in that (1) they often represent the only practical methods for certain transformations, (2) regioisomerically pure products can be obtained, and (3) the regiochemistry of alkylation can be controlled cleanly through generation of either mono- or dianions, as shown in eq. 4.182 (4.338).



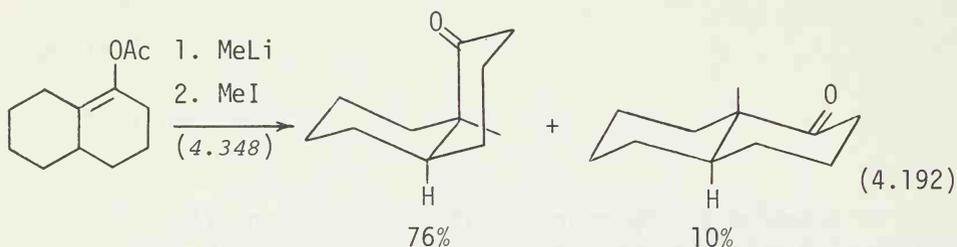
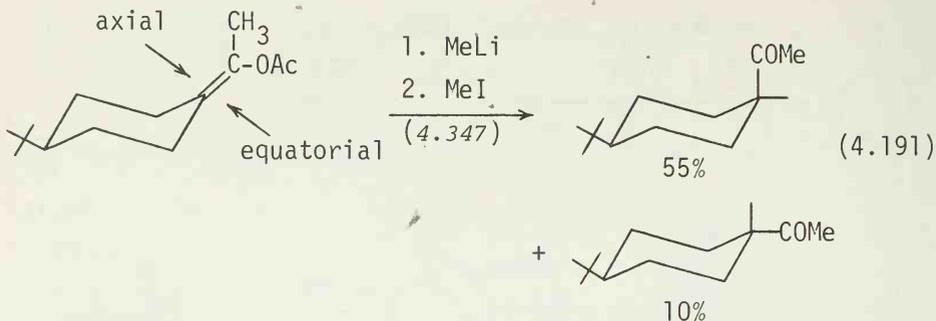
The alkylation of enolates with less reactive alkylating agents presents the above-mentioned problem of the formation of regioisomers as well as of poly-alkylated products. In principle, this problem can be solved by stopping or slowing down the equilibration of enolates without significantly retarding desired alkylation. One promising approach is to convert regio-defined potassium enolates into the corresponding potassium enoxytriethylborates prior to alkylation; see eqs. 4.187, 4.188 (4.344). Under these conditions, neither regiochemical scrambling nor poly-alkylation competes seriously with the desired mono-alkylation. If either lithium enolates or hindered trialkylboranes, such as *s*- Bu_3B , are used, the formation of enoxyborates either does not take place or is incomplete.



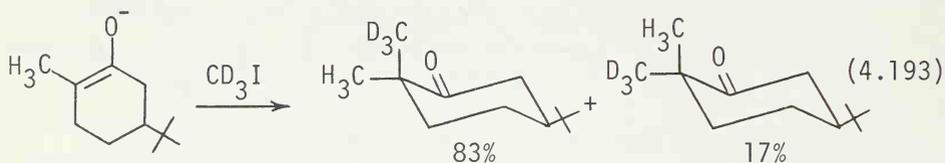
Alternatively, the reaction of regio-defined silyl enol ethers with alkyl halides can be promoted by certain fluorides; see eq. 4.189 (4.345), or TiCl_4 ; see eq. 4.190 (4.346). The latter reagent is unique in that it permits the hitherto difficult tertiary alkylation of ketones.



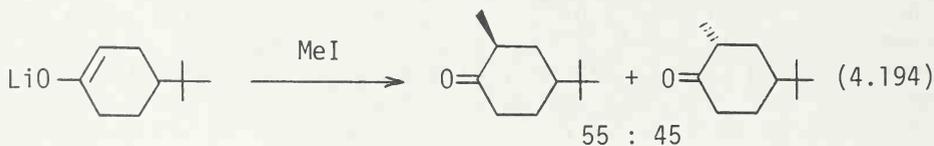
Stereochemistry of the Alkylation of Enolates. In cases where the steric requirements of the two sides of an enolate anion are considerably different, attack by an alkylating agent from the less hindered side is favored, as expected. The following two examples fall into this category. In analogy with the discussion presented in Sect. 4.3.2.2, the equatorial side of the methylene-cyclohexane system must be the less hindered side of the two.



Much less clear is the stereochemistry of the alkylation of endocyclic enolates. The available data suggest that the predominant attack takes place such that the entering alkyl group ends up as an axial substituent, as shown in eq. 4.193 (4.349).

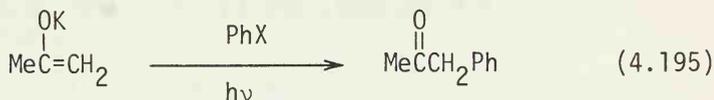


The results have been interpreted in terms of the stereoelectronically favorable arrangement in the axial attack relative to the equatorial attack. On the other hand, an essentially 50:50 mixture of *cis*- and *trans*-isomers is formed in the methylation of 4-*t*-butylcyclohexenolate; see eq. 4.194 (4.347).

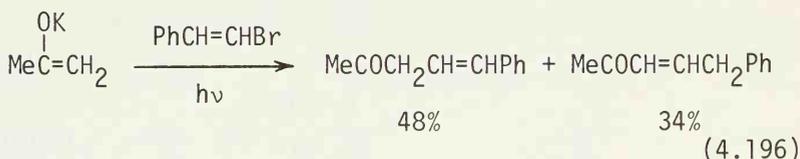


Although the significance of a twist-boat conformation was suggested, this explanation does not appear to be totally convincing. It should be noted that the products in eq. 4.194 are epimerizable under the reaction conditions, which is not the case in the three preceding reactions.

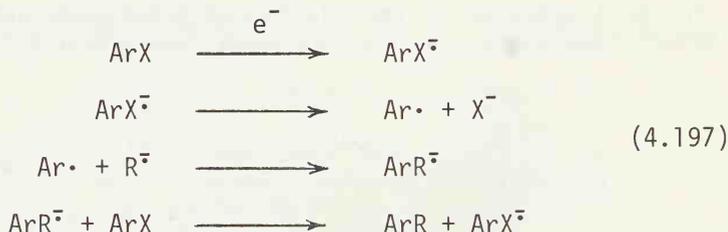
α -Arylation and α -Alkenylation. Until recently, the α -arylation and α -alkenylation of enolates had been very difficult. A few methods have recently been developed for these purposes. The most promising by far is Bunnett's photochemical arylation; see eq. 4.195 (4.350), and alkenylation; see eq. 4.196 (4.351).



X = Cl (68%), Br (52%), I (71%)

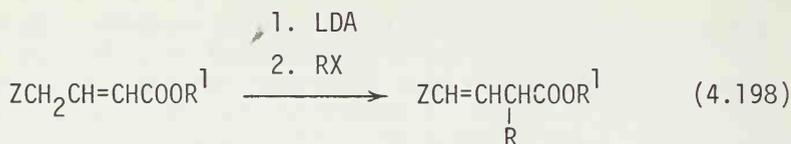


The results have been interpreted in terms of the $S_{\text{RN}}1$ mechanism; see eq. 4.197 (4.350).

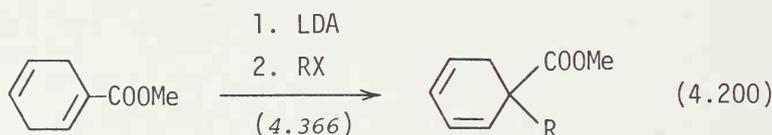
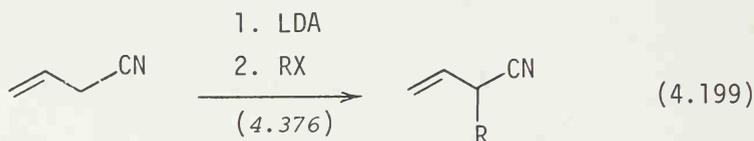


α -Alkylation of Aldehydes, Esters, Nitriles, and Other Related Compounds. Various aspects of the alkylation of ketones are presented in the above discussions. Some representative alkylation reactions of other carbonyl and related compounds are now briefly presented. The metallated derivatives of esters, aldehydes, and various related compounds are now readily available through appropriately strong but nonnucleophilic bases, as discussed in Sect. 4.3.4.1. In many cases, their alkylation proceeds satis-

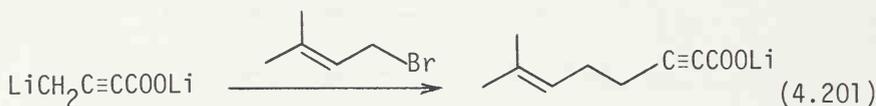
factorily, as summarized in Table 4.14. In most of the examples listed in Table 4.14, there is no ambiguity regarding the structures of the products. In the alkylation of dienolates, α -alkylation is strongly favored over γ -alkylation, as shown in eqs. 4.198 to 4.200.



Z = H (4.353), SMe (4.357), OMe (4.358)



In the alkylation of the dianion of 2-butyric acid, however, γ -alkylation is the predominant path; see eq. 4.201 (4.370).



The observed α -selectivity in alkylation is in sharp contrast with the γ -selectivity in various carbonyl addition reactions of the corresponding dienolates discussed in the following section. The use of heterocyclic masked enolates is discussed in Sect. 4.3.4.6.

Table 4.14. α -Alkylation of Aldehydes, Esters, Nitriles, and Other Related Compounds

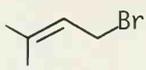
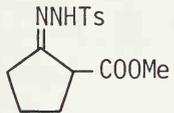
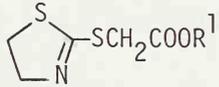
Carbonyl or Related Compound	Base	Alkylating Agent	Yield (%)	Ref.
(Aldehydes)				
R^1R^2CHCHO	KH		88 to 96	4.331
		<i>n</i> -RI	about 50	4.331
(Esters and Lactones)				
CH_3COO+	LICA	RX	42 to 96	4.329
<i>n</i> -PrCOOMe	LDA, THF	RX	88 to 98	4.352
MeCH=CHCOOEt	LDA, HMPA	RX	90 to 96	4.353
$+SCR^1R^2COOMe$	2 Li	MeI or PhCH ₂ Br	72 to 85	4.354
	LDA, THF	RX	>90%	4.355
<i>n</i> -C ₆ H ₁₃ CH=CHCOOMe	LiB(<i>bu-s</i>) ₃ H	RX	50 to 63	4.356
MeSCH ₂ CH=CHCOOMe	LDA	RX	63 to 92	4.357
MeOCH ₂ CH=CHCOOMe	LDA	RX	42 to 81	4.358
HOOCH ₂ COOEt	LICA	RX	50 to 98	4.359
PhCH=NCH ₂ COOEt	LDA	RX	75 to 90	4.360
PhCONHCH ₂ COOEt	2 LDA, TMEDA	RX	48 to 71	4.361
	3 LDA	RX	49 to 64	4.362
RCH(OH)COOEt	2 LDA	RX	57 to 79	4.363
Me ₂ NCH=NCHR ¹ COOMe	LDA	RX	65 to 84	4.364
	NaH, DMF	RX	34 to 68	4.365

Table 4.14 continued

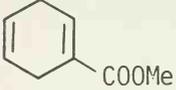
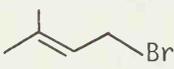
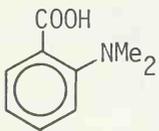
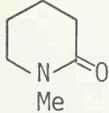
Carbonyl or Related Compound	Base	Alkylating Agent	Yield (%)	Ref.
	LDA	RX	52 to 96	4.366
(Carboxylic Acids)				
Me ₂ CHCOOH	2 LDA	RCH ₂ X	46 to 80	4.367
Me ₃ SiCH ₂ COOH	2 LDA	RX	60 to 95	4.368a
PhSCHR ¹ COOH	2 LDA	RX	95 to 98	4.368b
MeSCHR ¹ COOH	2 LDA	RX	59 to 80	4.369
MeC≡CCOOH	LiN 		53 to 59	4.370
R ¹ CH(COOH) ₂	3 <i>n</i> -BuLi	RX	74 to 88	4.371
PhCONHCH ₂ COOH	3 LDA	RX	23 to 60	4.361
	Li, NH ₃	RX	45 to 80	4.372
(Amides)				
	LDA or LiNMe ₂	RI	68 to 85	4.373
R ¹ R ² CHCONMe ₂	LiNEt ₂ , HMPA	RBr	69 to 86	4.374
MeCONMe ₂	LDA	MeI and PhCH ₂ Br	62 and 99	4.375

Table 4.14 continued

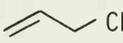
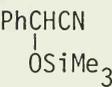
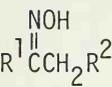
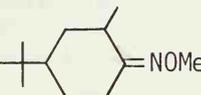
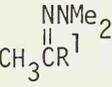
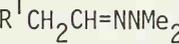
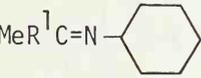
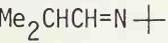
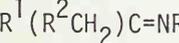
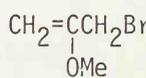
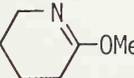
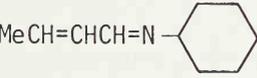
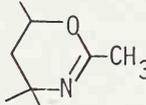
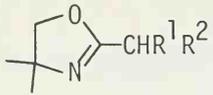
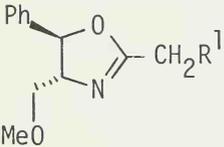
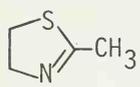
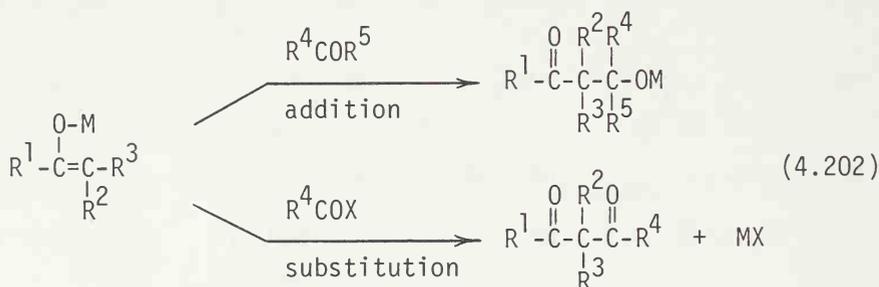
Carbonyl or Related Compound	Base	Alkylating Agent	Yield (%)	Ref.
(Nitriles)				
	LDA	RX	72 to 98	4.376
	LDA	RX	48 to 96	4.377
(Other masked carbonyl compounds)				
	2 BuLi	RX	37 to 81	4.378
	LDA	MeI	86 to 94	4.379
	LDA	RX	83 to 95	4.380
	LiNEt ₂	RBr	75 to 79	4.381a
	LiNEt ₂	RX	62 to 80	4.381b 4.381c
	LDA, DME	RBr	59 to 76	4.382
	LDA		43 to 84	4.383
	LDA, HMPA	RI	52 to 60	4.384
	LDA, HMPA	RX	98 to 100	4.385
	BuLi	RX	70 to 90	4.386

Table 4.14 continued

Carbonyl or Related Compound	Base	Alkylating Agent	Yield (%)	Ref.
	RLi	RX	60 to 75	4.387
	BuLi or LDA	RX	30 to 84	4.388
	BuLi	RX	80 to 95	4.389

4.3.4.3 Reactions of Enolates with Carbonyl Compounds

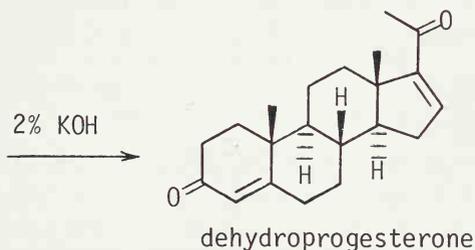
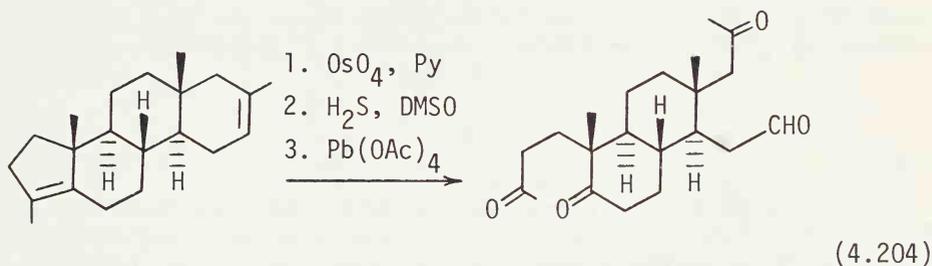
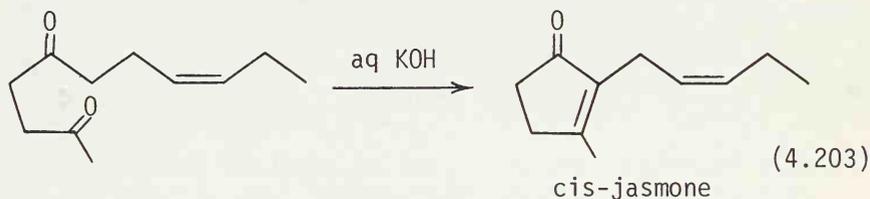
The reactions of enolates with carbonyl compounds may arbitrarily be divided into the following two types (eq. 4.202).



The aldol reaction (4.390) represents the addition reactions, and the Claisen condensation (4.391) represents the substitution reactions. Some representative addition and substitution reactions of enolates with carbonyl compounds is briefly discussed in this section, while the reaction of enolates with α,β -unsaturated carbonyl compounds, that is, the Michael reaction, is discussed in the following section.

The Aldol and Related Reactions. A wide variety of reactions of enolates with carbonyl compounds fall into the category of the aldol and related reactions.

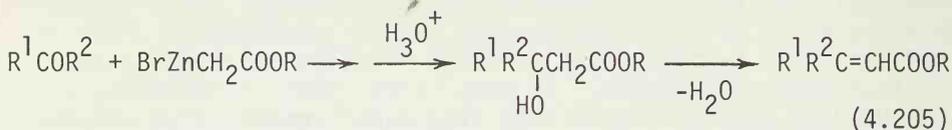
(a) The aldol reaction (4.390). The aldol reaction can be carried out under either acidic or basic conditions (4.390). The base-catalyzed aldol condensation is shown in eq. 4.202. On protonolysis the reaction produces β -hydroxy ketones which can be dehydrated to give α,β -unsaturated carbonyl compounds. Both β -hydroxy and α,β -unsaturated carbonyl moieties are found among various natural products. In many cases, their biogenesis is presumed to involve enzyme-catalyzed aldol condensation processes. The reaction has also played an important role in the laboratory synthesis of many natural products and related substances, especially those containing five- and six-membered rings, as shown in eqs. 4.203 (4.392) and 4.204 (4.393).



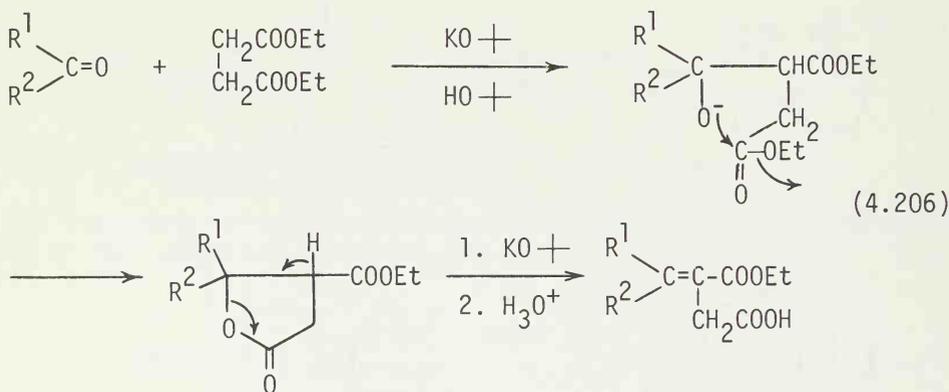
Despite its obvious significance, however, the aldol reaction has been plagued with various problems. Some of these problems and their possible solutions are discussed later in detail.

At this point it is useful to note that the following well-known name reactions may be considered variations of the aldol reactions.

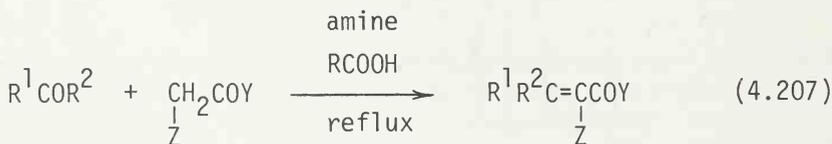
(b) The Reformatsky reaction (4.36, 4.37). The Reformatsky reaction may be viewed as the ester version of the aldol reaction.



(c) The Stobbe reaction (4.394). A variation of the Reformatsky reaction involving the use of potassium salt of ethyl succinate is called the Stobbe reaction.



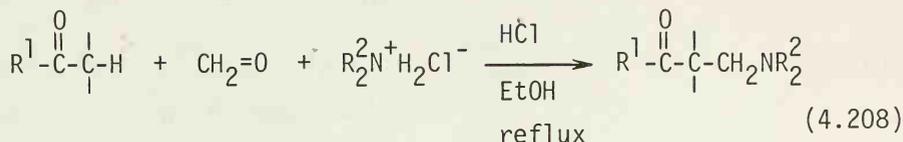
(d) The Knoevenagel reaction (4.395). Various reactions of relatively acidic carbonyl compounds with aldehydes and ketones are classified as the Knoevenagel reaction, which does not even require any metal containing reagent.



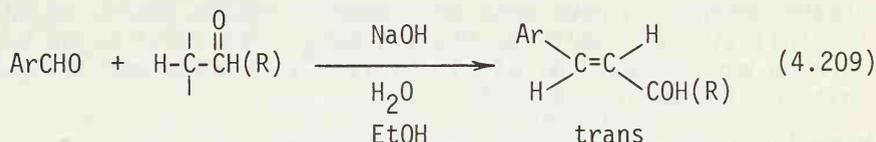
Y = R, OR, and so on; Z = COY, CN, Ph, NO₂, and so on

(e) The Mannich reaction (4.396). The aminomethylation of ketones, aldehydes and other related active hydrogen compounds is

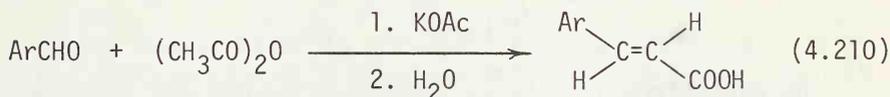
called the Mannich reaction. Its similarity to the aldol reaction in the reactant-product relationship is indicated in eq. 4.208.



(f) The Claisen-Schmidt reaction (4.397). This reaction represents nothing but a special case of the aldol reaction in which one of the carbonyl compounds is an aromatic aldehyde.

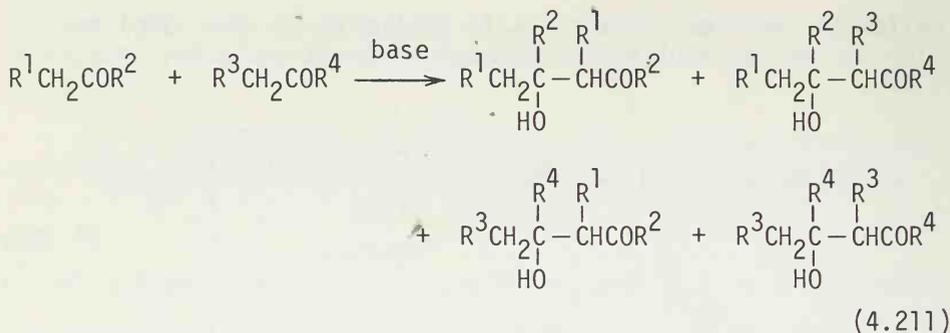


(g) The Perkin reaction (4.398). It should also be pointed out that various carbonyl olefination reactions, such as the Wadsworth-Emmons reaction and the Peterson reaction discussed in Sect. 4.3.3.3, and epoxidation reactions represented by the Darzens reaction (Sect. 4.3.3.4) are closely related to the aldol reaction.

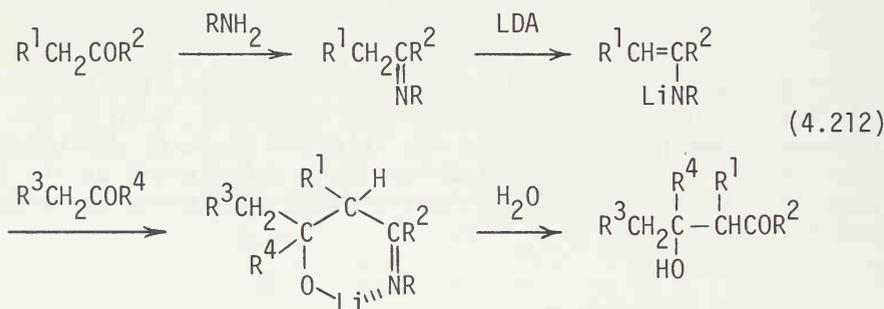


Problems and Solutions in the Aldol Reaction. Of various problems associated with the aldol reaction, the following three are discussed in some detail: (1) cross/homo ratio, (2) regioselectivity, and (3) stereoselectivity.

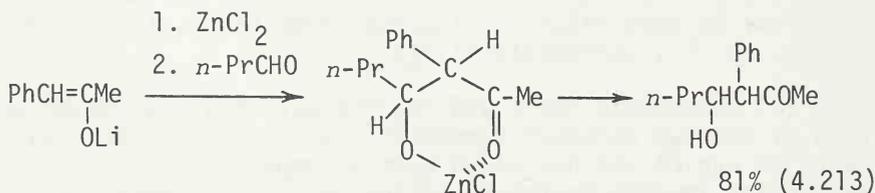
(a) Cross/homo ratio and regioselectivity. In cases where both of the two carbonyl compounds are enolizable, the aldol reaction can be and has often been accompanied by cross-homo scrambling leading to the formation of all four possible products, as shown in eq. 4.211.



It is therefore important to be able to direct the reaction so that only one cross-aldol product is obtained. A number of selective procedures have been developed in recent years, of which the following are worth mentioning here. The first major breakthrough was achieved by Wittig (4.399) with preformed lithium salts of imines (eq. 4.212).

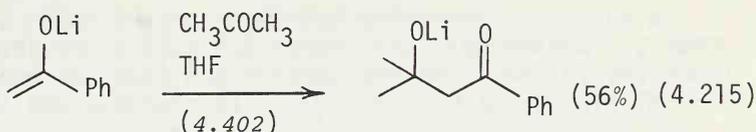
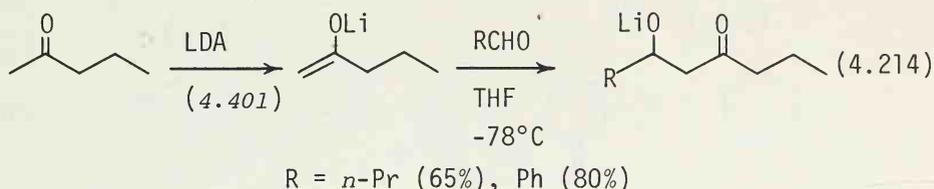


An operationally more convenient procedure for cross-aldol condensation has been developed by House (4.400), which involves the reaction of preformed lithium enolates with aldehydes in the presence of $ZnCl_2$ or $MgCl_2$, as shown in eq. 4.213.

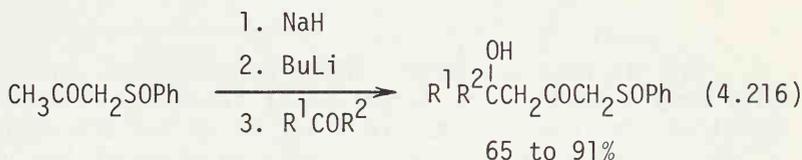


The aldol reaction can be further complicated by regiochemical scrambling. It has been reported, however, that, as in alkyl-

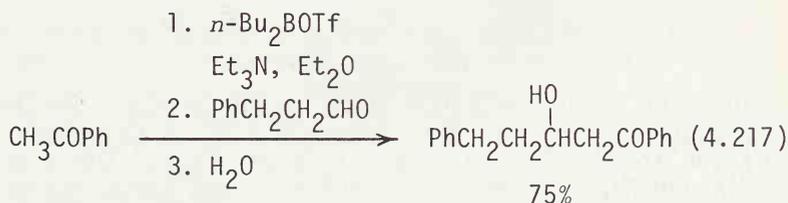
ation (Sect. 4.3.4.2), even regio-unstable "kinetic" enolates can undergo regio-specific aldol reactions when the desired aldol processes are sufficiently rapid.



An indirect but potentially highly useful approach by Kuwajima (4.403) involves the reaction of dianions of β -ketosulfoxides with aldehydes and ketones (eq. 4.216). The products can be further converted into a variety of cross-aldol derivatives.

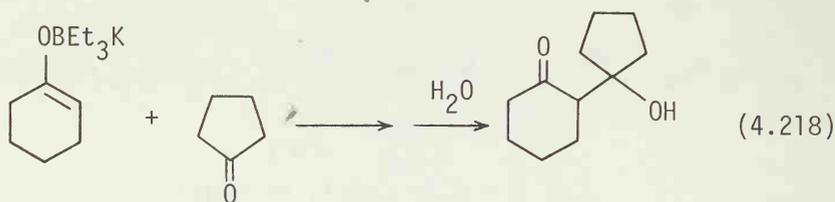


A more recent trend in the aldol reaction is to use metal enolates containing highly covalent metal-oxygen bonds, such as B-O and Si-O. Thus Mukaiyama and others (4.404) have developed selective procedures involving the intermediacy of enoxyboranes, as shown in eq. 4.217.

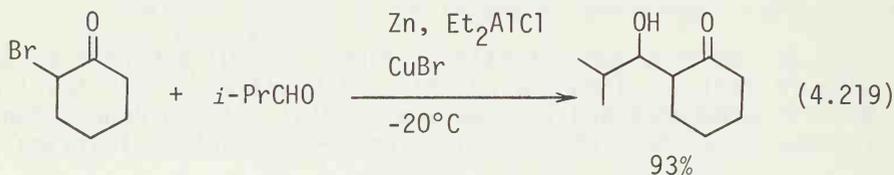


Although not yet fully developed, the following aldol reaction of potassium enoxytrialkylborates discovered in our laboratories

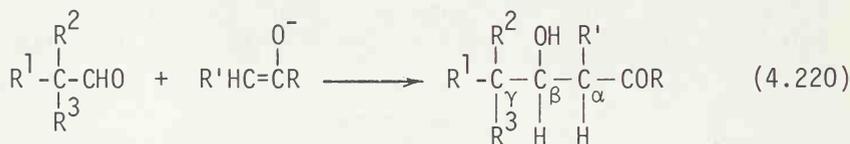
appears to be readily applicable to the hitherto difficult selective ketone-ketone condensation, as shown in eq. 4.218 (4.405).



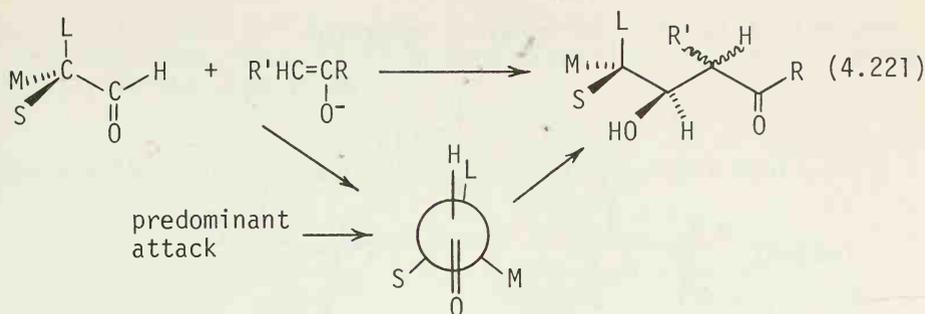
Also highly promising are the aldol reaction of silyl enol ethers, promoted by TiCl₄ (Sect. 6.4.2.2) or by trialkylammonium fluorides (4.406), and the copper- and aluminum-moderated reaction of zinc enolates; see eq. 4.219, for example (4.407).



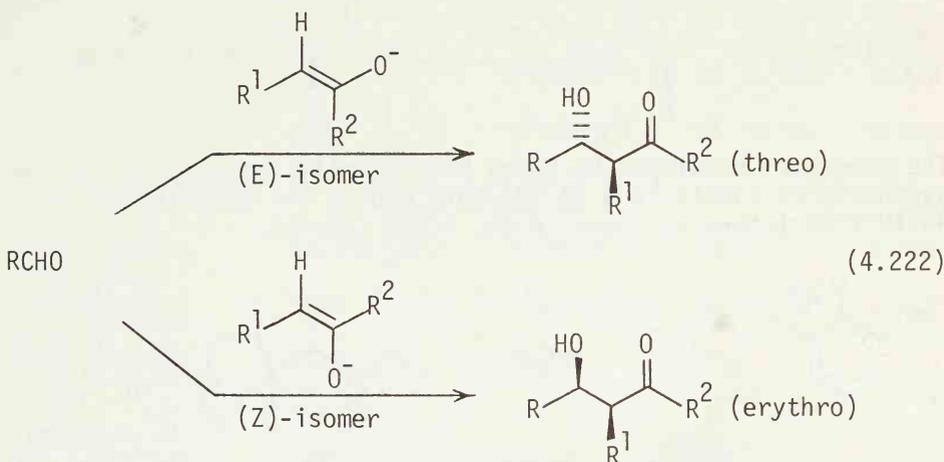
(b) Stereoselectivity. Aldol condensation can be additionally complicated by the formation of stereoisomeric mixtures. Consider, for example, the reaction of an enolate derived from a primary alkyl ketone (R¹CH₂COR) with an aldehyde having an asymmetric carbon atom in the α-position (R¹R²R³CCHO), which proceeds cleanly as in eq. 4.220.



Since the α- and β-carbon atoms in the product can be either R or S, there can be four diastereomers even in the event that the γ-carbon atom is 100% R or S. In such a case, the stereochemical relationship between the α- and β-carbon atoms, as well as between the β- and γ-carbon atoms, must be considered. The available data suggest that the relationship between the β- and γ-carbon atoms may be predicted based on Cram's rule (Sect. 4.3.2.2), as depicted in eq. 4.221.



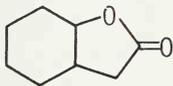
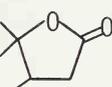
Much less clear is the relation between the α - and β -carbon atoms. At least three distinct stereochemical results have been reported. Dubois (4.408) and Heathcock (4.409) have found that aldol condensation is subject to kinetic stereoselection, with (E)- and (Z)-enolates giving exclusively or predominantly the threo and erythro aldols, respectively (eq. 4.222).



On the other hand, the completely opposite stereospecificity, that is, (E) \rightarrow erythro and (Z) \rightarrow threo, has been reported for the reaction of enoxydimethylalanes and acetaldehyde (4.410). Finally, House (4.400) has reported a nonstereospecific but stereoselective aldol reaction which is carried out under the influence of ZnCl_2 or MgBr_2 . Under such conditions, the threo isomer corresponding to the six-membered metal chelate intermediate with the greater number of equatorial substituents predominates, regardless of the enolate geometry (eq. 4.223).

marized in Table 4.15. In the reaction of dienolates with carbonyl compounds, carbon-carbon bond formation takes place predominantly in the γ -position.

Table 4.15. Miscellaneous Variations of the Aldol Reaction

Enolate Precursor	Base	Carbonyl Compound	Product Yield (%)	Ref.
(Esters and lactones)				
$\text{CH}_3\text{COOBu-}t$	LICA	R^1COR^2	high	4.412
	Li	$\text{R}^1\text{COH(R}^2)$	about 70	4.413
$\text{CH}_3\text{COSBu-}t$	LDA	$\text{R}^1\text{COH(R}^2)$	68 to 80	4.414
$\text{XCH}_2\text{CO}_2\text{Bu-}t$	LDA	$\text{R}^1\text{COH(R}^2)$	65 to 85	4.415
(X=OBu- <i>t</i> , NMe ₂)				
$\text{BrCH}_2\text{CO}_2\text{Et}$	active Zn	$\text{R}^1\text{COH(R}^2)$	95 to 98	4.416
$\text{C}\equiv\text{NCH}_2\text{COOR}$	BuLi	$\text{R}^1\text{COH(R}^2)$	55 to 83	4.417
MeCH=CHCOOEt	LICA	Me_2CO	78	4.418
	LDA	CH_2O	95	4.419a
	LDA	CO_2	75	4.419b
(Acids)				
R^1CHCOOH Br	Zn	$\text{R}^2\text{C}\equiv\text{N}$	63 to 77	4.420

(continued...)

Table 4.15 continued

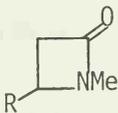
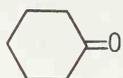
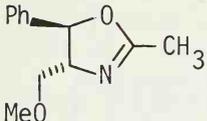
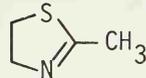
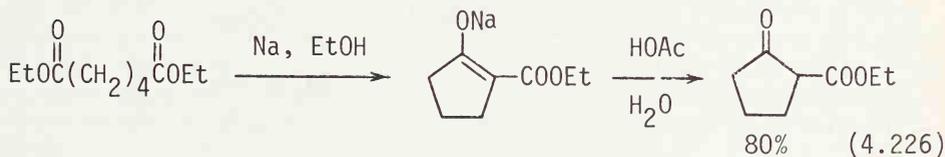
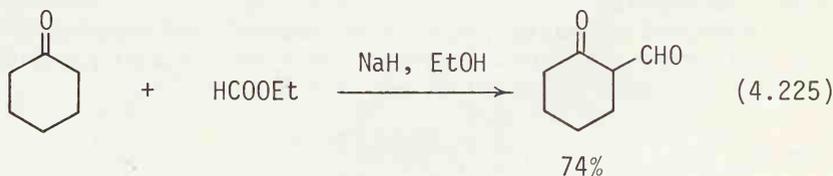
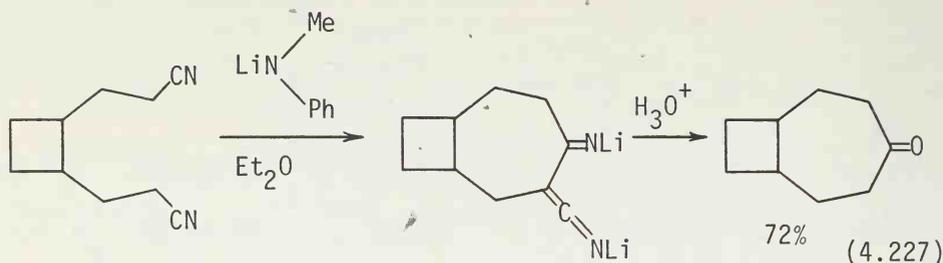
Enolate Precursor	Base	Carbonyl Compound	Product Yield (%)	Ref.
$R^1R^2CHCOOH$	$BrMgN(Pr-i)_2$	$R^3COH(R^4)$	43 to 88	4.421
$Me_2C=C(Br)COOH$	2 BuLi (-100°C)	R^1COR^2	30 to 64	4.422
$MeCH=CHCOOH$	$LiNEt_2$	R^1COR^2	48 to 64	4.423
(Amides)				
	LDA	R^1COR^2	55 to 88	4.424
$R^1R^2CHCONEt_2$	$BrMgN(Pr-i)_2$	R^3COH	85 to 88	4.421
$R^1R^2CHCONMe_2$	$LiNEt_2$	$R^3COH(R^4)$	39 to 91	4.425
$MeCONMe_2$	LDA	$R^1COH(R^2)$	97 to 99	4.375
(Nitriles)				
CH_3CN	$NaOC_8H_{17-n}$		70	4.426
R^1R^2CHCN	$LiNEt_2$	$R^3COH(R^4)$	70 to 96	4.427
$PhCHCN$ $OSiMe_3$	LDA	$R^1COH(R^2)$	96 to 100	4.428
(Other masked carbonyl compounds)				
$CH_2=CHNH-$ 	LDA	RCN	71 to 91	4.429
$PhCH_2C(=NNHTs)Me$	MeLi	R^1COR^2	-	4.430
$R^1C(=NNHTs)C(=O)R^2$	3 BuLi	$R^3COH(R^4)$	48 to 78	4.431

Table 4.15 continued

Enolate Precursor	Base	Carbonyl Compound	Product Yield (%)	Ref.
$R^1 \overset{\text{NOH}}{\text{C}} \text{CH}_2 \text{R}^2$	2 BuLi	$R^3 \text{COH}(\text{R}^4)$	45 to 55	4.378b
$R^1 \text{R}^2 \text{CHCH}=\text{NNMe}_2$	LiNEt ₂	$R^3 \text{COR}^4$	87 to 90	4.432
$\text{Me}_3\text{SiCHR}^1\text{CH}=\text{NX}$ (X=Bu-t, NMe ₂)	LDA	$R^2\text{CHO}$	88 to 94	4.433
	BuLi	RCHO	-	4.434
	n-BuLi	$R^1 \text{COR}^2$	-	4.435

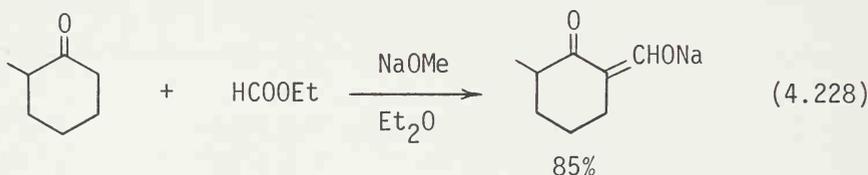
The Claisen Condensation and Related Reactions. Since the results of earlier investigations of the Claisen, eq. 4.225 (4.391), Dieckmann, eq. 4.226 (4.436), and Thope-Ziegler, eq. 4.227 (4.436), reactions have been extensively reviewed, no detailed discussion of these relatively well-established reactions is presented. The following comments may be of use, however, in applying these reactions to organic synthesis.





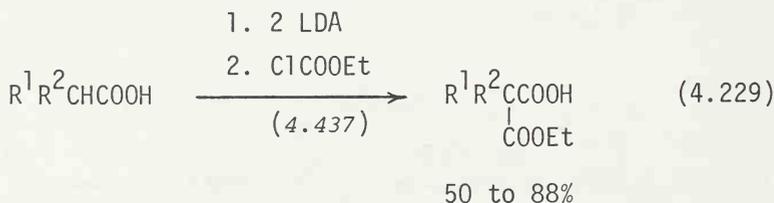
The Claisen condensation is an equilibrium reaction that tends to reverse itself in many cases. This difficulty can, in principle, be overcome by shifting the equilibrium through metalation of the 1,3-dicarbonyl product.

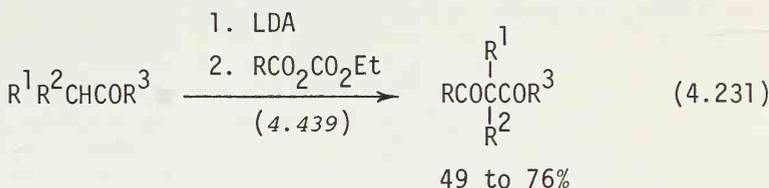
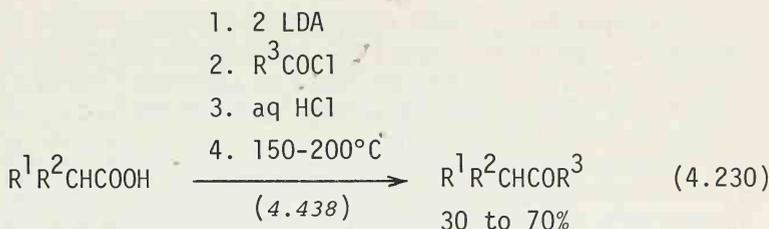
Under equilibrating conditions, the Claisen condensation may give mixtures of cross- and homo-condensation products. On the other hand, the regioselectivity of the Claisen condensation carried out under these conditions can often be distinctly higher than that in the alkylation of the same enolate, as shown in eq. 4.228 (4.336).



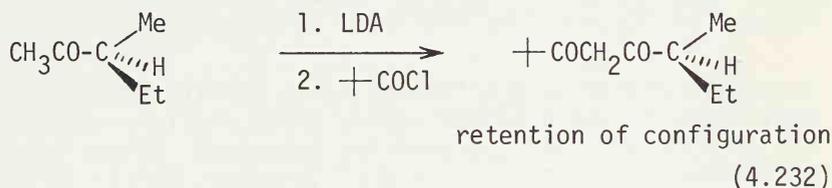
In contrast to the corresponding alkylation, the Claisen condensation tends to take place exclusively or predominantly in the less hindered α -position which has been interpreted in terms of the relative stability of the enolates of two possible 1,3-dicarbonyl compounds.

A recent trend in the Claisen and related reactions is to use preformed metal enolates and reactive acylating agents, such as acyl halides, as shown in eq. 4.229 to 4.231.



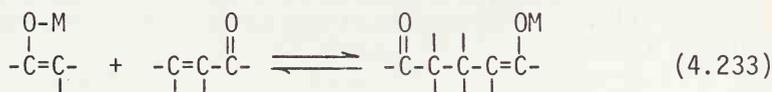


It is noteworthy that, under these kinetic conditions, even race-mizable chiral centers can retain much of their chirality, as shown in eq. 4.232 (4.440).



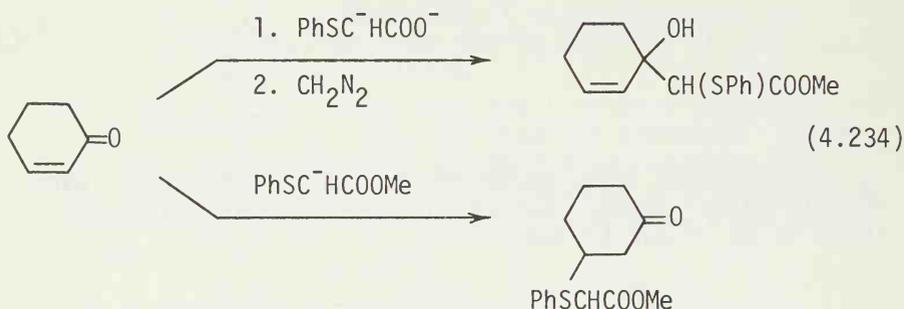
4.3.4.4 The Michael Reaction

The Michael Reaction and the Robinson Annulation Reaction. The conjugate addition of enolate anions to α,β -unsaturated carbonyl and related compounds is known as the Michael reaction; see eq. 4.233 (4.441).



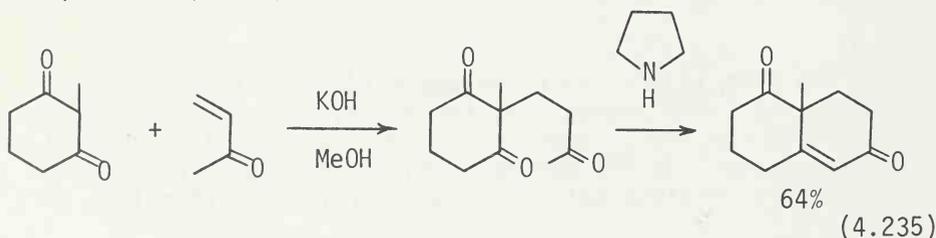
As is the case in any other conjugate addition reaction of organometallics, the products of the Michael reaction are metal enolates that can participate in various reactions that typical enolates undergo. Unlike the reaction of "ordinary" proximally nonfunctional organoalkali and organoalkaline earth metals with

α,β -unsaturated carbonyl compounds, in which the 1,2-addition path tends to predominate, the corresponding reaction of metal enolates usually undergoes the 1,4-addition. Although it is not completely clear, the above-mentioned difference, in part, must be due to the charge delocalized or "soft" nature of enolates, the effects of which are at least twofold. Firstly, the softness of enolates should favor attack at the soft olefinic site. It is instructive to note that the dianions of free carboxylic acids incapable of effective charge delocalization tend to undergo 1,2-addition, as shown in eq. 4.234 (4.442).



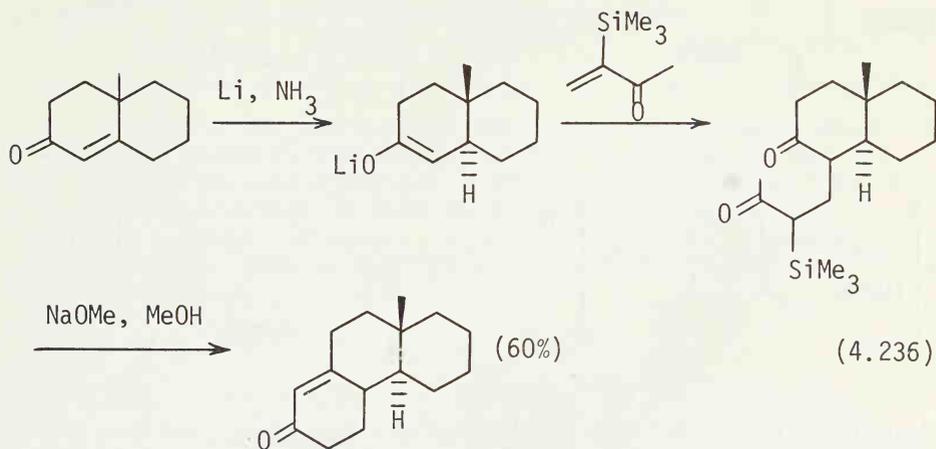
Secondly, charge delocalization makes enolate anions relatively weak bases in the Brønsted sense, which should promote the reversal of both 1,2- and 1,4-addition processes. Under equilibrating conditions, the formation of the 1,4-adduct should be favored, as discussed in Sect. 4.3.2.4.

The Michael reaction represents one of the most widely used carbon-carbon bond-forming reactions. Particularly attractive from the viewpoint of natural product synthesis is the combination of the Michael reaction with the aldol reaction, known as the Robinson annulation (4.443). In favorable cases, the Michael reaction and the Robinson annulation proceed quite satisfactorily. Thus, for example, relatively acidic carbonyl compounds, such as 2-methyl-1,3-cyclohexanedione, can be converted into Michael adducts and annulated products in high yields, as shown in eq. 4.235 (4.444).



With less acidic carbonyl compounds the Michael reaction tends to be complicated by various problems including (1) polymerization of α,β -unsaturated carbonyl compounds, (2) regiochemical scrambling, (3) the reverse Michael reaction, and (4) competition arising from the aldol, Claisen, and other reactions of enolates. Various procedures have been developed to circumvent these difficulties. An early trend was to use the mildest possible bases, such as amines and hydroxides, and to run the reaction in protic solvents in order to minimize certain side reactions. Other early modifications include (1) the use of the Mannich bases (4.445) and β -halo ketones as precursors of enones and (2) the use of enamines (4.446) in place of metal enolates. For extensive discussions of these older techniques, the reader is referred to reviews by Bergamann (4.441), House (4.316), and Jung (4.339a).

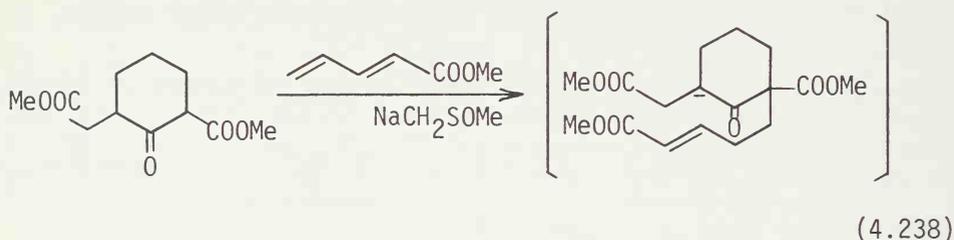
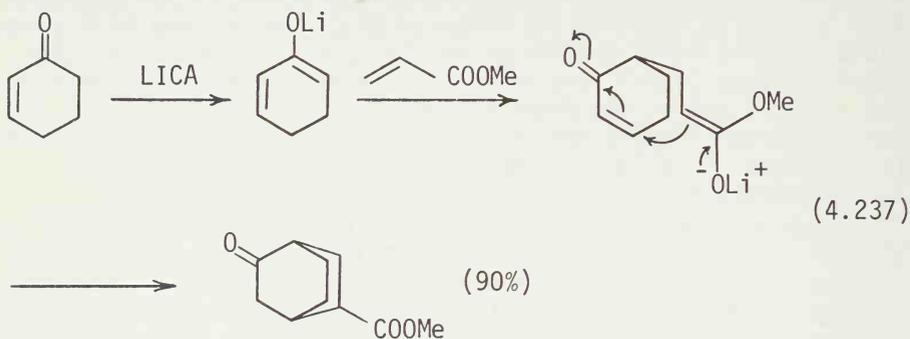
None of the above modifications, however, permits clean regioselective trapping of "kinetic" enolates by α,β -unsaturated carbonyl compounds, which would require generation of "kinetic" enolates under aprotic conditions and their consumption via the desired conjugate addition at rates faster than undesirable side reactions. This was first achieved by Stork (4.447) with α -silylated enones, such as methyl α -trimethylsilylvinyl ketone, as shown in eq. 4.236.



The trimethylsilyl group presumably accelerates the Michael reaction through its anion-stabilizing effect and, perhaps more importantly, retards the polymerization of the enone through its steric hindrance. The results shown in eq. 4.236 indicate that the desired Michael reaction is faster than the regio-isomeriza-

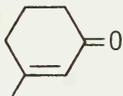
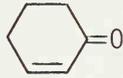
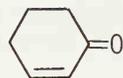
tion of the "kinetic" enolate intermediate.

Another recent trend in the area of annulation is to use the alkylation of enolates as a more flexible substitute for the Michael reaction, as discussed in Sect. 4.3.4.2. Taking advantage of the fact that the product of the Michael reaction is an enolate, the following efficient syntheses of bicyclic; see eq. 4.237 (4.448), and tricyclic; see eq. 4.238 (4.449), compounds involving the double Michael annulation have been achieved.

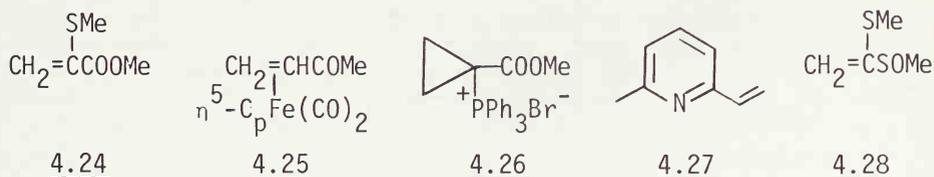


Miscellaneous Variations of the Michael Reaction. Various α -hetero-substituted enolates have successfully been used in the Michael reaction. The structures of some α -hetero-substituted enolates are shown in Table 4.16.

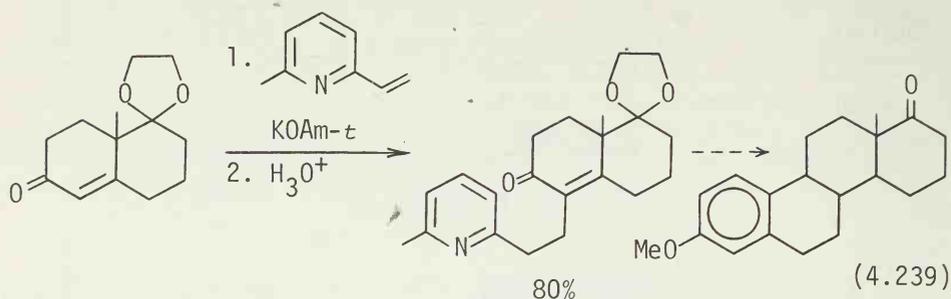
Table 4.16. The Use of α -Hetero-Substituted Enolates in the Michael Reaction

Enolate	Acceptor	Yield (%)	Ref.
$\begin{array}{c} \text{ONa} \\ \\ \text{MeOC}=\text{C}(\text{SEt})_2 \end{array}$	$\text{H}_2\text{C}=\text{CHCOX}$ (X = Me, OMe, O <i>Bu-t</i>)	92 to 95	4.211
$\begin{array}{c} \text{LiO} \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{EtO} \end{array} \begin{array}{c} \text{S} \\ \\ \text{S} \end{array}$	$\begin{array}{c} \text{MeC}=\text{CHCOOEt} \\ \\ \text{Cl} \end{array}$	80	4.204
$\begin{array}{c} \text{MN}=\text{C}=\text{C} \\ \diagdown \\ \text{OR} \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array}$		90	4.450
$\begin{array}{c} \text{LiO} \\ \diagdown \\ \text{C}=\text{CHN}=\text{CHPh} \\ \diagup \\ \text{EtO} \end{array}$		90	4.451
$\begin{array}{c} \text{LiN}=\text{C}=\text{C} \\ \diagdown \\ \text{SePh} \end{array} \begin{array}{c} \diagup \\ \diagdown \end{array} \begin{array}{c} \text{C}_6\text{H}_{13} \end{array}$		91	4.452

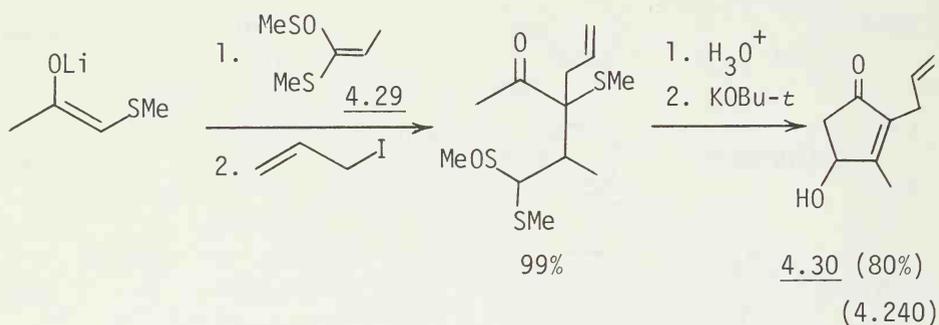
In addition to the α -silyl enones, α -sulfur-substituted α,β -unsaturated carbonyl compounds, such as 4.24 (4.453), have also been used as Michael acceptors. Other noteworthy additions to the list of acceptors include an iron π -complex 4.25 (4.454), cyclopropyl ketones and esters, such as 4.26 (4.455), 2-vinyl-6-methylpyridine, such as 4.27 (4.456), and a vinyl sulfide sulfoxide 4.28 (4.457).



The 2-vinylpyridine derivative (4.27) has been developed as an efficient bis-annulating agent; see eq. 4.239 (4.456).

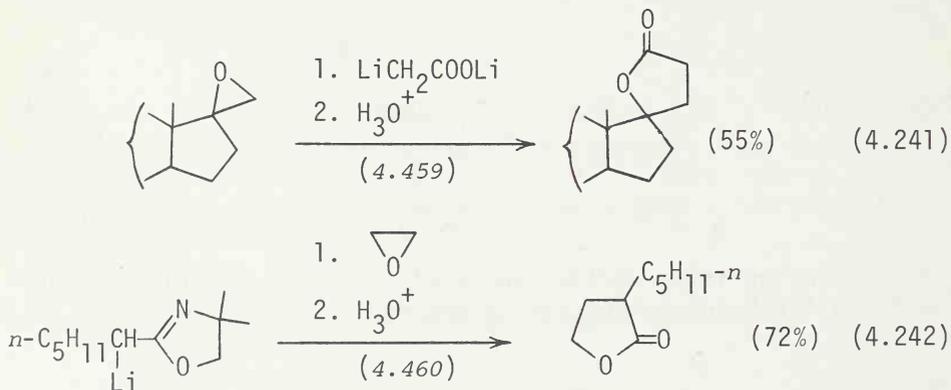


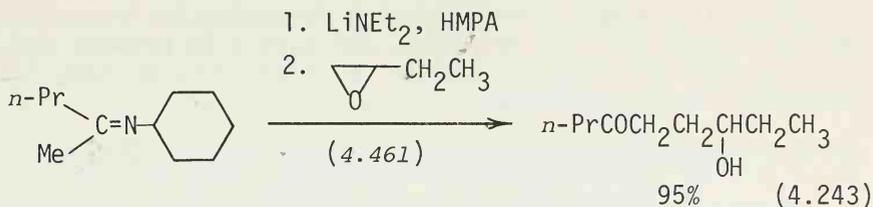
A vinyl sulfide sulfoxide 4.29 has been used in an efficient synthesis of 4.30; see eq. 4.240 (4.458).



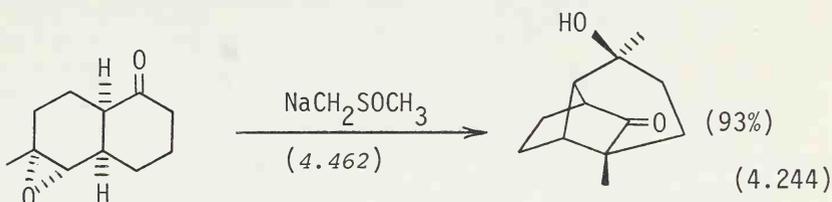
4.3.4.5 Reactions of Metal Enolates and Related Compounds with Epoxides

As shown in Scheme 4.6, the reaction of enolates with epoxides produces γ -hydroxy carbonyl compounds. A few noteworthy examples follow (eqs. 4.241 to 4.244).

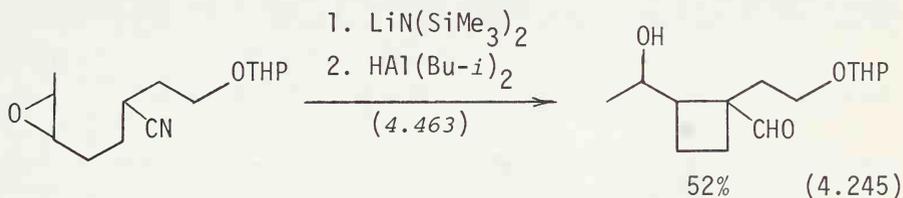




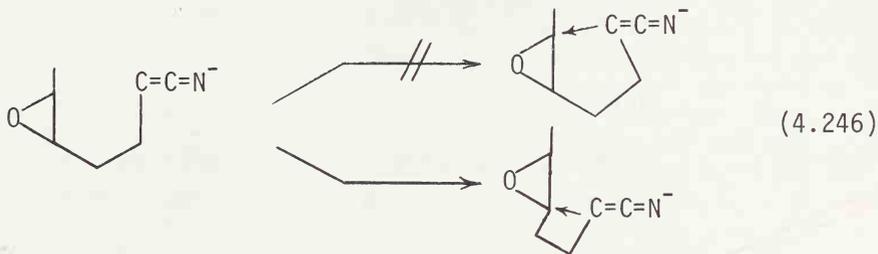
Note that the reaction shown in eq. 4.243 is readily applicable to the synthesis of 1,4-diketones.



Very interesting results have been observed in the epoxy-nitrile cyclization, which can be explained in terms of stereoelectronic constraints (4.463). For example, the four-membered ring formation is favored over the usually favored five-membered ring formation in the reaction shown in eq. 4.245 (4.463b).



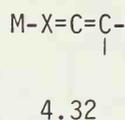
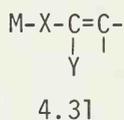
The back-side attack at the tertiary carbon atom of the epoxide ring leading to the five-membered ring formation is not competitive, presumably because the carbanionic center cannot readily reach around and attack the tertiary carbon from the side opposite the oxygen atom, as depicted in eq. 4.246.



As expected, the three-membered ring formation is favored over the four-membered ring formation, and partition between the five- and six-membered rings appears to be governed by various factors including steric hindrance.

4.3.4.6 Carbon-Carbon Bond Formation via Masked Enolates

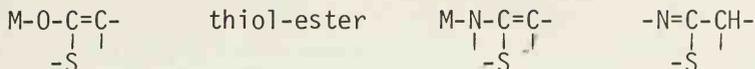
The chemistry of metal enolates can, in principle, be expanded by changing various structural parameters of the metal enolates. A priori, any metal-containing species that may be classified either as metal enolates or their hetero analogues would be represented by either 4.31 or 4.32.



In reality, metallated nitriles appear to be the only readily accessible species represented by 4.32. Similarly, only O, N, and S can be X in 4.31. Interestingly, few species represented by 4.31 in which X is S have been developed as useful reagents or intermediates in organic synthesis. We therefore restrict our discussion to those species represented by 4.31 in which X is either O (4.31a) or N (4.31b). On the other hand, various elements including C, N, O, and S can be Y, as shown in Table 4.17.

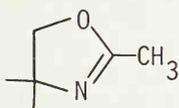
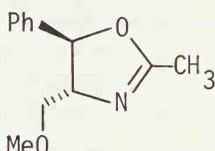
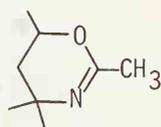
Table 4.17. Metal Enolates and Masked Metal Enolates

Structure	Organic Precursors	Structure	Organic Precursors
$\begin{array}{c} \text{M-O-C=C-} \\ \quad \\ \text{-C-} \\ \end{array}$	aldehydes, ketones	$\begin{array}{c} \text{M-N-C=C-} \\ \quad \quad \\ \text{-C-} \\ \end{array}$	imines, oximes, hydrazones, and so on
$\begin{array}{c} \text{M-O-C=C-} \\ \quad \\ \text{-O} \end{array}$	acids, esters, lactones	$\begin{array}{c} \text{M-N-C=C-} \\ \quad \quad \\ \text{-O} \end{array}$	-N=C-CH- -O
$\begin{array}{c} \text{M-O-C=C-} \\ \quad \\ \text{N} \\ \quad \end{array}$	amides, lactam	$\begin{array}{c} \text{M-N-C=C-} \\ \quad \quad \\ \text{N} \\ \quad \end{array}$	-N=C-CH- N

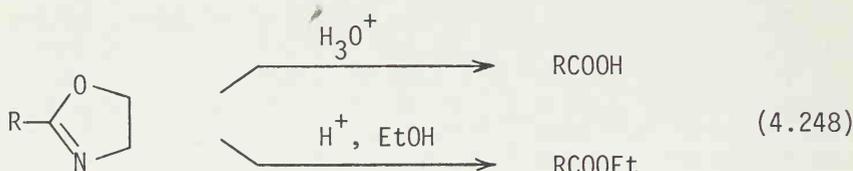
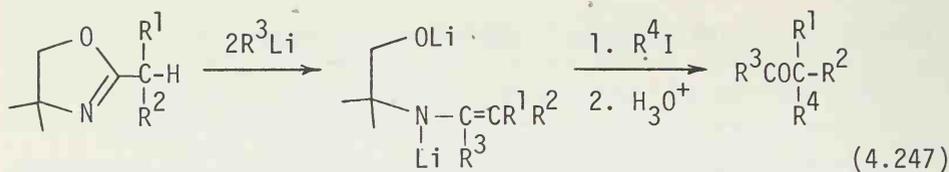


If the metallated thiol-esters are excluded, the chemistry of 4.31a has now been reasonably well established, as discussed in several preceding sections. On the other hand, active and systematic investigations of the chemistry of 4.31b are largely of recent origin. For the sake of convenience, we arbitrarily term the metallated nitriles and species represented by 4.31b masked metal enolates. Many examples of these species are listed in Tables 4.14 and 4.15, and a few of their reactions have already been discussed in Sects. 4.3.4.2 to 4.3.4.5. In this section, we focus our attention on just one well-investigated case, that is, the chemistry of oxazolines and dihydro-1,3-oxazines, which seems to represent new directions in the chemistry of enolates. Although not discussed here, it may be pointed out that investigations of metal enolates and their masked analogues containing various metals other than Group IA and Group II elements, such as B, Al, Si, Sn, and transition metals, also appear to be a promising area.

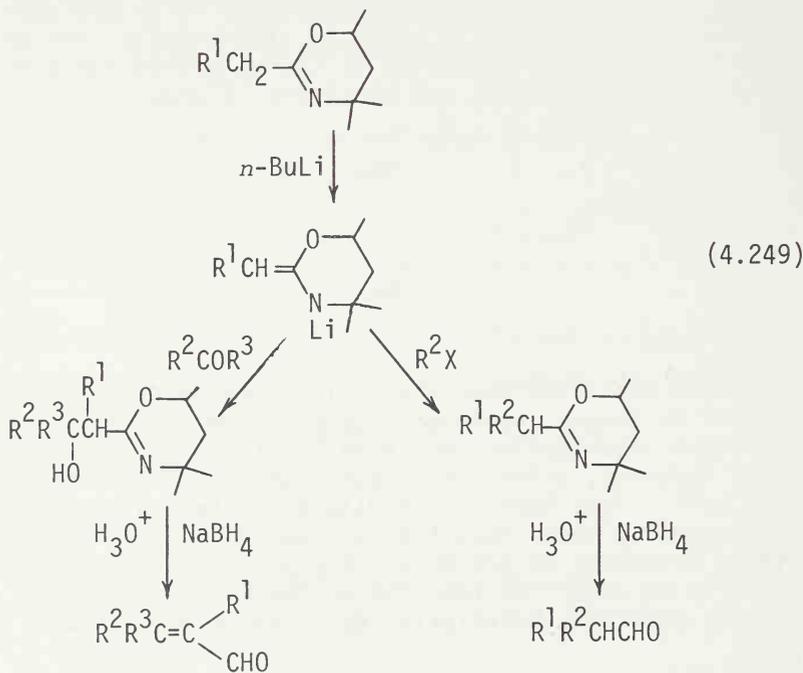
Carbon-Carbon Bond Formation via Oxazolines and Dihydro-1,3-oxazines. Over the past decade Meyers and his associates have developed oxazolines, 4.33 and 4.34, for example, and dihydro-1,3-oxazines, 4.35, for example, as useful masked enolates. Several reviews on the subject are available (4.464, 4.465).

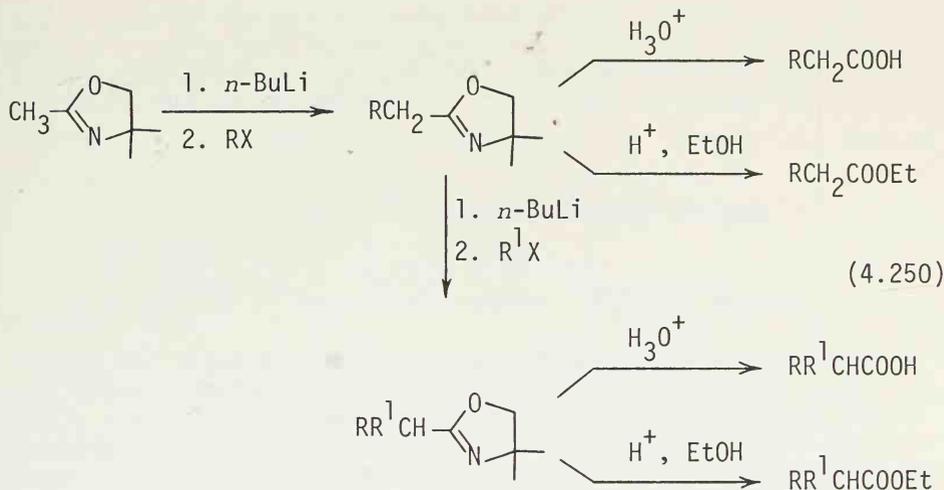
4.334.344.35

The oxazoline and dihydro-1,3-oxazine rings are relatively stable to bases. Although organolithiums can attack the C=N bond of these heterocycles (eq. 4.247), it is generally inert to Grignard reagents, unless it is converted to the corresponding iminium salt. Thus their reactivity as masked carbonyl derivatives is generally lower than that of cyanides. On the other hand, these heterocycles are relatively sensitive to acids and can readily be converted into the corresponding carboxylic acids and esters on acidic solvolysis, as shown in eq. 4.248.



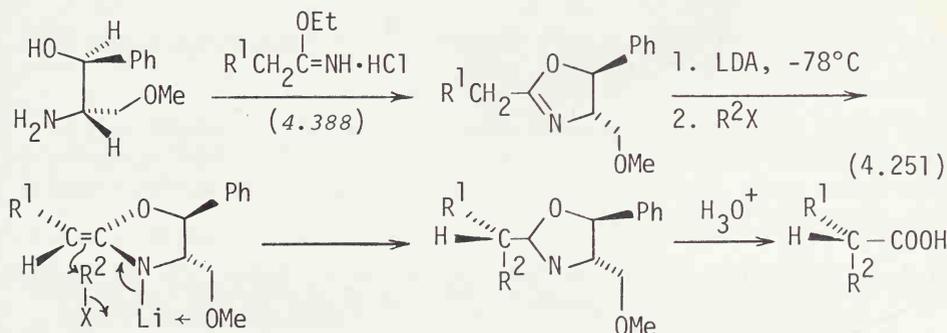
Alternatively, dihydro-1,3-oxazines can be converted into aldehydes via reduction with NaBH_4 followed by hydrolysis. Furthermore, the α -hydrogen atom of an alkyl substituent in the 2-position can readily be abstracted with strong bases, such as *n*-BuLi and LDA. These properties can now be exploited in developing various procedures for the syntheses of aldehydes, as shown in eq. 4.249 (4.386), ketones, as shown in eq. 4.247 (4.387a), carboxylic acids and esters, as shown in eq. 4.250 (4.387b), and lactones, as shown in eq. 4.242 (4.460).

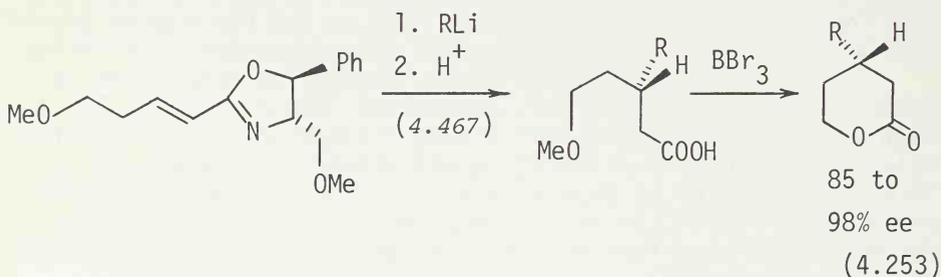
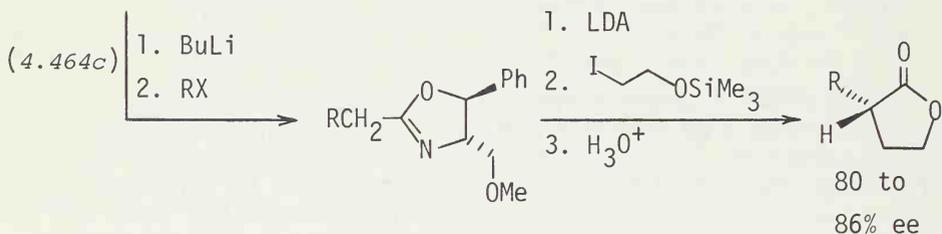
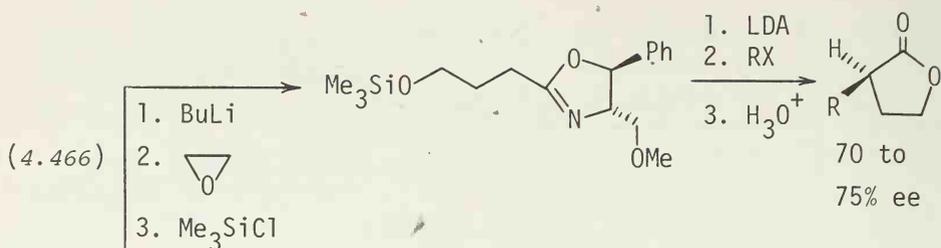




The results shown above indicate that the whole of enolate chemistry could be rewritten using 1,3-oxazolines and dihydro-1,3-oxazines as masked carbonyl compounds. One critical question that might be raised here is whether or not it is necessary or desirable to attempt to do so. This author believes that the development of new procedures for carbon-carbon bond formation is still a viable research project so long as the procedures developed are satisfactory and offer some unique synthetic utilities.

Recent investigations by Meyers have established that certain readily available chiral oxazolines, for example, 4.34, are highly promising reagents for asymmetric carbon-carbon bond formation. For a highly stimulating discussion, the reader is referred to a review by Meyers (4.464c). The following examples represent a few of the as yet very small number of asymmetric carbon-carbon bond-forming reactions that may be considered useful (ee > 70 to 80%).





4.4 CARBON-HETERO ATOM BOND FORMATION VIA ORGANOALKALI AND ORGANOALKALINE EARTH METALS

The metal atom of the metal-carbon bond of organoalkali and organoalkaline earth metals can be replaced with either nonmetallic elements, such as H, N, O, P, S, and halogens, or various metallic elements (transmetalation).

4.4.1 Formation of Carbon-Hydrogen Bonds -- Reduction of Organic Compounds via Organometallics of Group IA and Group II Elements

metal reduction generally involves a series of one-electron transfer steps, while reduction with metal hydrides, including catalytic hydrogenation, usually, but not always, involves two-electron transfer reactions.

Metals. The metals used commonly in the dissolving metal reduction include Li, Na, K, Mg, Ca, Zn, Al, Sn, Ti, and Fe. The versatility of the alkali and alkaline earth metals in the dissolving metal reduction stems from the fact that they are readily oxidized to the corresponding cations, as indicated by their low ionization energies (Appendix IV) and by their high oxidation potentials (Table 4.18).

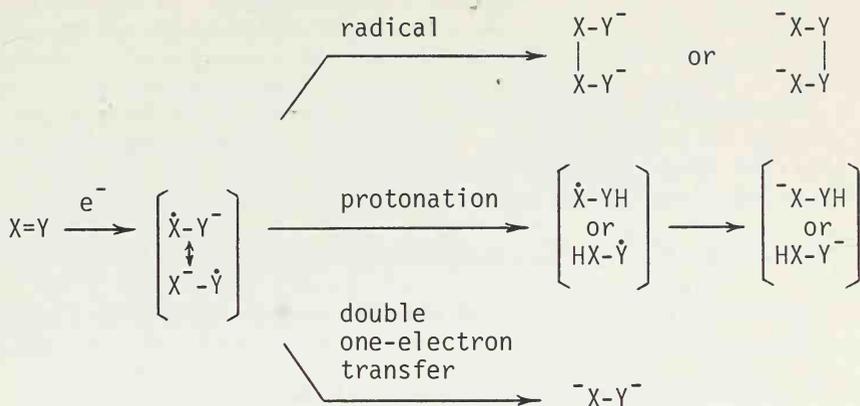
Table 4.18. Oxidation Potentials^a (in liquid NH₃ at 25°C)

Reaction	ϵ^0 (V)
Li \longrightarrow Li ⁺ + e ⁻	+2.34
Na \longrightarrow Na ⁺ + e ⁻	+1.89
K \longrightarrow K ⁺ + e ⁻	+2.04
Mg \longrightarrow Mg ⁺² + 2e ⁻	+1.74
Ca \longrightarrow Ca ⁺² + 2e ⁻	+2.17
Zn \longrightarrow Zn ⁺² + 2e ⁻	+0.54

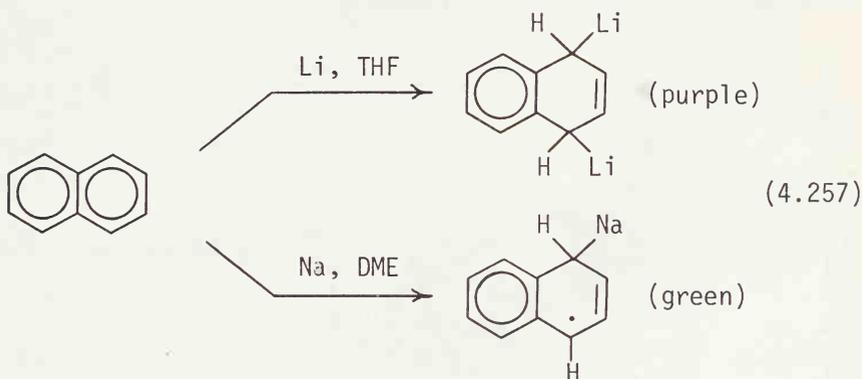
^aThe oxidation potentials in the table are taken from Jolly, W. L., *J. Chem. Educ.*, **33**, 512 (1956).

General Scheme and Selection of Proton Donors. Both multiple bonds and single bonds have been reduced with dissolving metals. Although the exact course of reduction depends on a number of factors, including metals, proton donors, and solvents, the general scheme for the dissolving metal reduction may be represented by Scheme 4.9. For the sake of simplicity, only the scheme for the double bond reduction is shown. The scheme for the reduction of single or triple bonds may be obtained by deleting or adding one X-Y bond, respectively.

Scheme 4.9



Of the three paths shown in Scheme 4.9, the double one-electron transfer process is relatively uncommon and appears to be practically limited to cases where the electrostatic repulsion between the two negatively charged centers can be minimized (1) through delocalization, (2) by the formation of tight ion pairs or highly covalent species, or (3) by the use of solvents of low dielectric constant. A typical example is shown in eq. 4.257 (4.469).



The relative rates of radical coupling and protonation reactions can be controlled most readily by controlling the rate of protonation which, in turn, can be achieved by choosing an appropriate proton donor. In the absence of a substance that can act as an efficient proton donor, radical coupling becomes the pre-

dominant reaction path. Even if a proton donor is used, radical coupling can still be a serious side reaction. Effective suppression of radical coupling can, in principle, be achieved by promoting protonation through the use of strong acids. Unfortunately, however, metals of high oxidation potentials are readily decomposed by strong acids, which severely restricts the selection of proton donors. From the practical viewpoint, the dissolving metal reductions may be classified into the following four categories according to the proton donor used:

1. Reduction with metals and protic acids ($pK_a < 10$).
2. Reduction with metals and neutral protic compounds (pK_a 15 to 30),
3. Reduction with metals and protic bases ($pK_a > 30$),
4. Reduction with metals in aprotic solvents.

Reduction Potential of the Organic Substrates. It is essential to select a proper reagent combination that best suits the desired transformation. In addition to the parameters discussed above, the reduction potential of the organic substrate, which can be quantitatively expressed in terms of the polarographic half-wave reduction potential defined as shown in Fig. 4.1, is an important criterion in this respect.

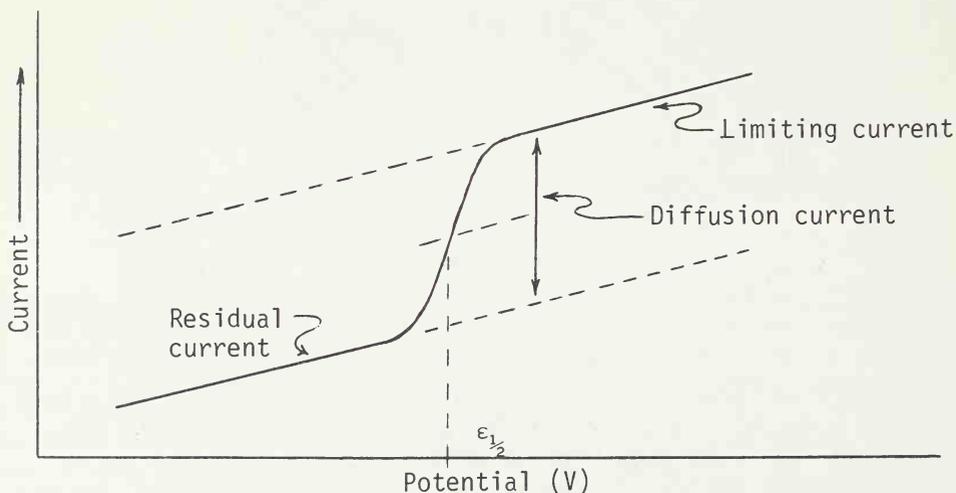
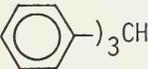
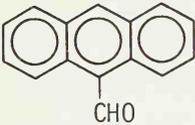
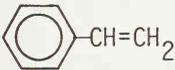
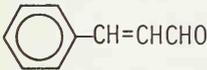
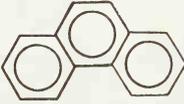
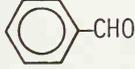
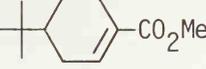
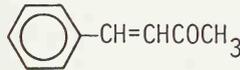


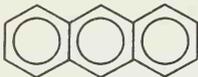
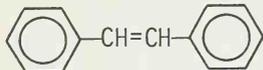
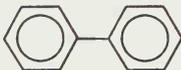
Fig. 4.1. Polarographic half-wave reduction potential ($E_{1/2}$)

When the electrode potential is low, only the residual current is observed. As it approaches the reduction potential of the substrate, a rapid reduction, which is reflected by a sudden increase in current, is observed. It reaches the limiting value, however, as the reduction becomes of diffusion control. The electrode potential corresponding to the half-way point of the diffusion current is defined as the polarographic half-wave potential ($\epsilon_{1/2}$). The reduction potential is a measure of the electron affinity, that is, the energy liberated when an electron is added to the substrate. Thus it should be roughly proportional to the energy of the lowest unoccupied molecular orbital (LUMO).

Table 4.19 lists the half-wave reduction potentials of some organic substances versus a standard calomel electrode (SCE). The smaller the absolute value is, the easier the reduction is.

Table 4.19. The Half-Wave Reduction Potentials of Some Organic Compounds^a

Compound	$\epsilon_{1/2}$ versus SCE	Compound	$\epsilon_{1/2}$ versus SCE
	-1.05	$\text{CH}_3\text{CH}=\text{CHCO}_2\text{Me}$	-2.33 ^b
	-1.21		-2.37
	-1.34		-2.46
	-1.59		-2.50 ^b
	-1.64 ^b		-2.55 ^b

	-1.96	$\text{CH}_2=\text{CHCH}=\text{CH}_2$	-2.63
	-2.16		-2.70

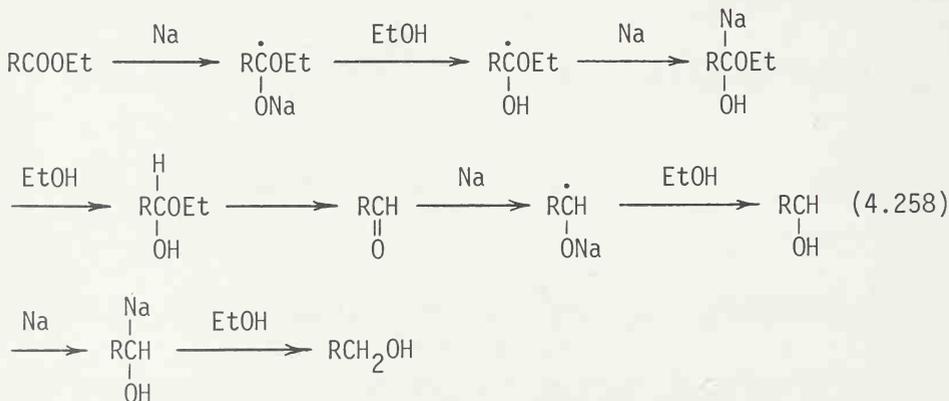
^aUnless otherwise noted, the values are taken from Streitwieser, A., Jr., *Molecular Orbital Theory for Organic Chemists*, John Wiley & Sons, New York, 1961.

^bHouse, H. O., *Acc. Chem. Res.*, 9, 59 (1976).

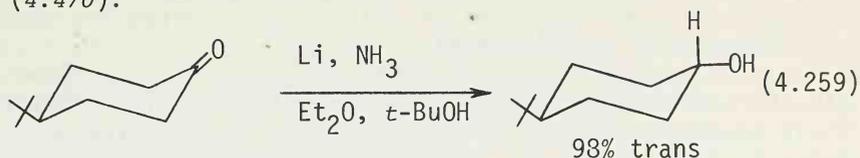
The following discussion of specific dissolving metal reductions and related reactions is very brief. For further details, the reader is referred to a textbook by House (4.316) and references cited in this section.

4.4.1.2 Reduction of Carbonyl Compounds with Alkali and Alkaline Earth Metals

The Bouveault-Blanc and Related Reductions. Aldehydes, ketones, and esters can be reduced to alcohols with alkali metals in the presence of alcohols, such as EtOH, used as proton donors. The reduction of esters by this method is called the Bouveault-Blanc reduction which most likely proceeds by the following mechanism (eq. 4.258).



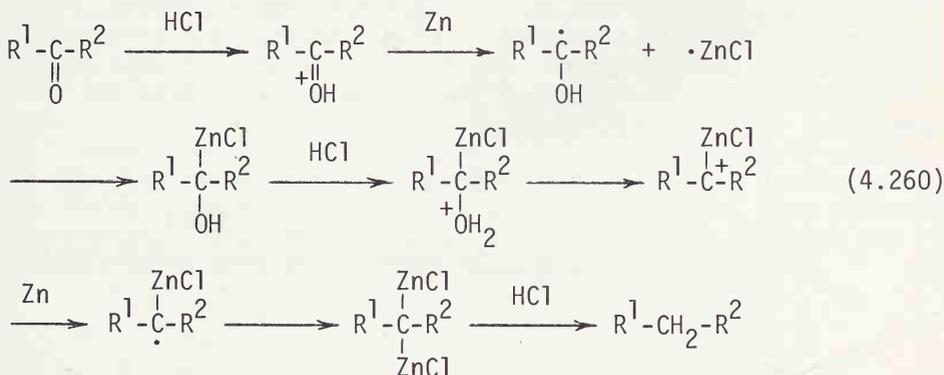
Similar mechanisms may be written for the reduction of aldehydes and ketones. The dissolving metal reduction of ketones tends to produce thermodynamically more stable products, as shown in eq. 4.259 (4.470).



In this respect, the dissolving metal reduction is often complementary with the metal hydride reduction, which tends to give the thermodynamically less stable isomers (Sect. 5.2.3.6).

The Clemmensen Reduction. In the presence of efficient proton donors, such as HCl, the reduction of ketones and aldehydes with zinc amalgam can produce the corresponding methylene and methyl compounds, respectively. The Clemmensen reduction has been reviewed in a comprehensive manner by Martin and Vedejs (4.471). The reaction is commonly run in a three-phase system consisting of zinc amalgam, aqueous HCl, and a nonpolar organic solvent, such as toluene, to minimize unwanted radical coupling. Amalgamation of zinc raises its hydrogen overvoltage to the point where it can resist the attack by HCl. Hydrogen halides are about the only strong acids whose anions are not reduced by zinc amalgam. It should be noted that the potential required for reduction of ketones in strong acidic media is substantially less (ca. -1.0 V) than that in neutral media (-2.0 to -2.5 V).

The mechanism of the Clemmensen reduction is unclear, since alcohols are not reduced under the Clemmensen conditions, they cannot be intermediates. The reaction is often complicated by skeletal rearrangements. The following scheme is based on the one that was proposed in the literature; see eq. 4.260 (4.472).



The intermediacy of a carbocationic intermediate in the above mechanism is consistent with frequently observed skeletal rearrangements. Any of the organozinc intermediates shown in eq. 4.260 can be protonolyzed under the reaction conditions. Thus various minor modifications of the above mechanism may also be considered as plausible paths.

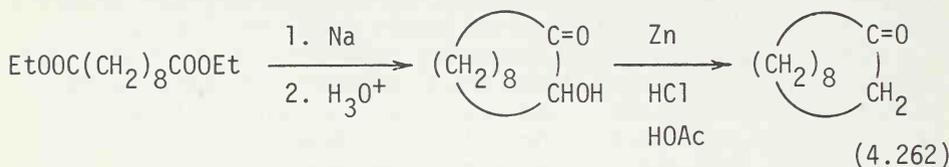
It is useful to know that the deoxygenation of ketones can also be achieved by various other methods including (1) the Wolff-Kishner reduction, (2) treatment of tosylhydrazones with NaBH_3CN (Sect. 5.2.3.6), (3) reduction of ketones to alcohols followed by tosylation and reduction with LiAlH_4 or LiBR_3N (Sect. 5.2.3.6), and (4) conversion of ketones into thioketals followed by hydrogenation over Raney nickel (Sect. 10.1.3).

The reduction of α -halo, α -hydroxy, and α -acetoxy ketones with zinc and HOAc follows a different reaction path, the overall change being the removal of the α -hetero substituents (eq. 4.261).

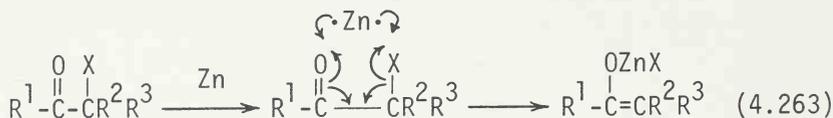


X = halogen, OH, OAc, and so on

The reaction can be used in tandem with the acyloin reaction for the conversion of dicarboxylic acid esters into cyclic ketones, as shown in eq. 4.262 (4.473).

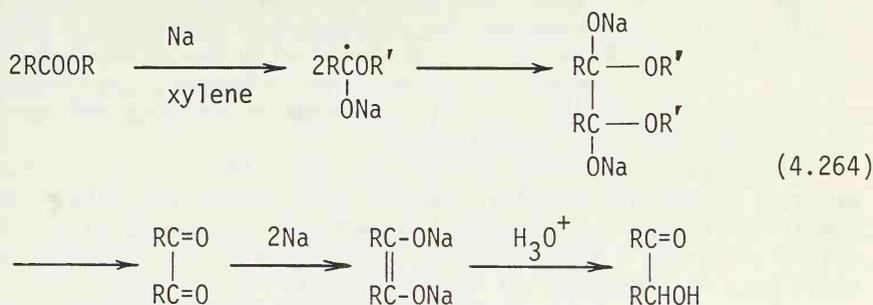


The mechanism of the reaction has not been clarified. It may involve the initial attack by zinc either at the carbonyl group, as in the Clemmensen reduction, or at the C-X bond. Alternatively, zinc may interact simultaneously with both the carbonyl and the C-X bond, as shown in eq. 4.263.

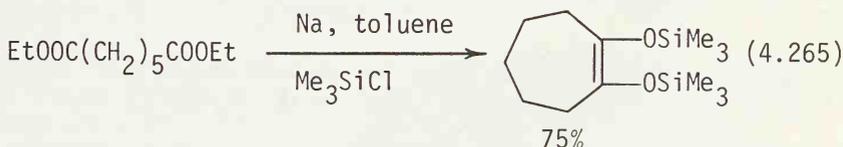


The Acyloin Reaction and Related Reactions. In the absence of efficient proton donors, the radical coupling process predominates. The reductive coupling of esters with sodium gives acyloins (4.474). Unlike essentially all other known cyclization reactions of chain molecules, the acyloin reaction can readily produce medium ring carbocycles in high yields. The synthesis of large rings by ordinary cyclization reactions requires the use of either the high dilution technique or other special reaction conditions. On the other hand, the acyloin reaction does not require such special reaction conditions.

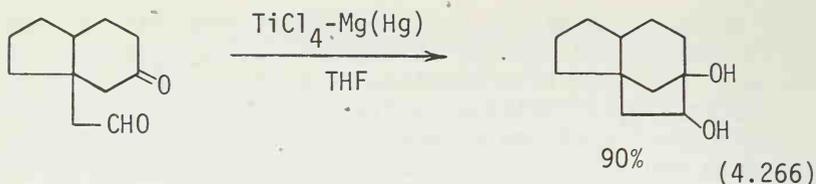
The reaction presumably proceeds by the mechanism shown in eq. 4.264.



Although small and common rings (four- to seven- membered) can also be prepared by the acyloin reaction, the Dieckmann cyclization reaction (4.475) induced by the endiolate intermediate tends to be competitive in these cases. This problem, however, can be alleviated by trapping the endiolate intermediate with Me_3SiCl , as shown in eq. 4.265 (4.476).



Reduction of ketones with alkali and alkaline earth metals in the absence of proton donors produces pinacols. In the past, Mg, Mg(Hg), and Al(Hg) have been used extensively. More recently, however, the combined use of Mg(Hg) and TiCl_4 has been recommended for this transformation; see eq. 4.266 (4.477).

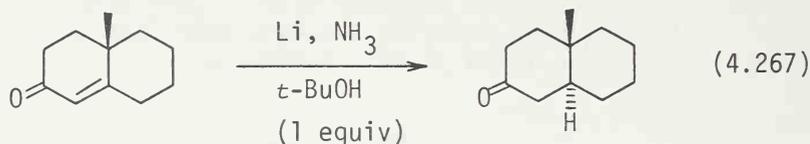


4.4.1.3 Reduction of Alkenes, Alkynes, and Arenes with Alkali and Alkaline Earth Metals

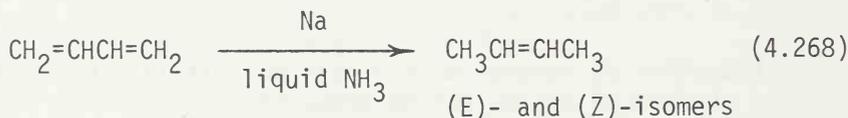
Alkenes. Simple alkenes are not readily reduced with dissolving metals. They can, however, be reduced with sodium in a mixture of *t*-BuOH and HMPA at 25°C (4.478). A wide variety of olefins, such as 1-hexene, methylenecyclohexane, 3-hexene, cyclohexene, norbornene, and $\Delta^{9,10}$ -octalin, have been reduced to the corresponding alkanes and cycloalkanes.

Alkenyl groups that are conjugated with carbonyl, alkenyl, or aryl groups are readily reduced with dissolving alkali metals. The reduction of α,β -unsaturated carbonyl compounds with alkali metals provides a regiospecific route to the corresponding metal enolates, as discussed in Sect. 4.3.4.1.

In contrast with catalytic hydrogenation (Sect. 10.1.3), the dissolving metal reduction of α,β -unsaturated ketones generally produces thermodynamically more stable stereoisomers, as shown in eq. 4.267 (4.327).

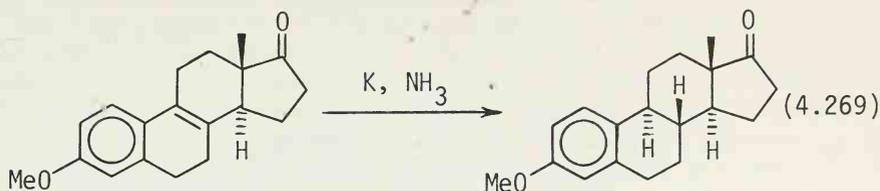


Conjugated dienes can be readily reduced with alkali metals, as exemplified by the reaction shown in eq. 4.268 (4.479).



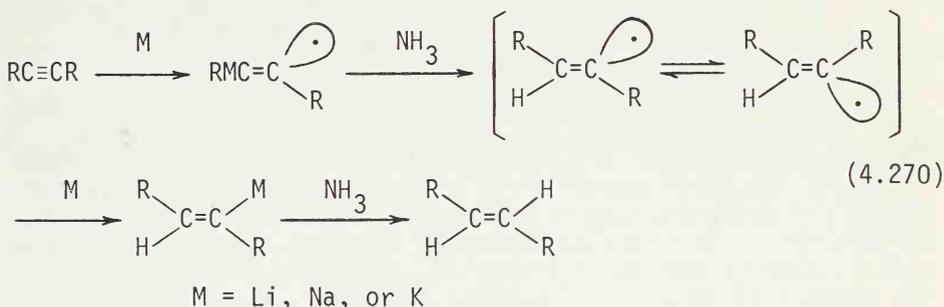
Styrene and its derivatives can also be reduced with alkali metals. This reaction provides an important procedure that has been used for the synthesis of 19-norsteroids; see eq. 4.269

(4.480), including a number of oral contraceptives.



The more stable *trans* isomer is formed selectively.

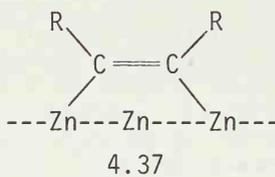
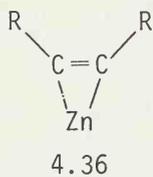
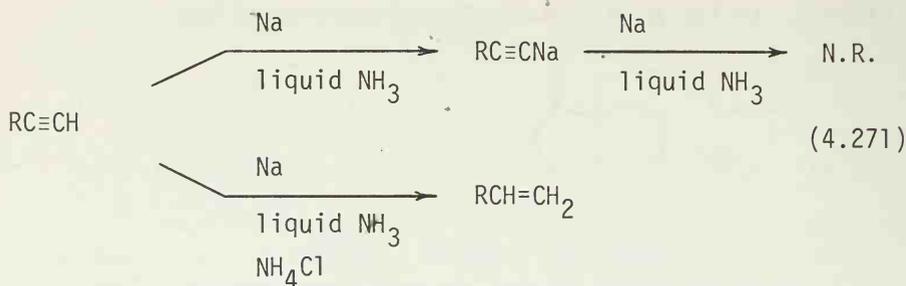
Acetylenes. Internal acetylenes are readily reduced to *trans*-olefins with alkali metals in liquid NH_3 . The reaction most probably proceeds by the mechanism shown in eq. 4.270.



Trans stereochemistry may be explained based on reasonable assumptions that the *trans*-alkenyl radical is the more stable stereoisomer and that it is this isomer that is converted into the configurationally rigid alkenylmetal intermediate with retention. With respect to stereoselectivity, the reaction is complementary with the catalytic hydrogenation over Lindlar's catalyst (Sect. 10.1.3).

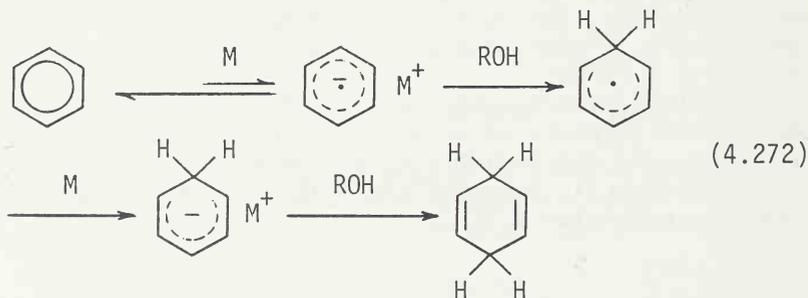
In the absence of an efficient proton donor, terminal acetylenes are converted to metal acetylides which are resistant to the attack by alkali metals in liquid NH_3 . In the presence of NH_4Cl , however, the formation of metal acetylides can be prevented, and the terminal acetylenes can also be converted into olefins (eq. 4.271).

It has recently been reported that internal acetylenes can be reduced to *cis*-olefins with zinc powder in 50% aq 1-propanol (4.481). *Cis* stereochemistry can be explained in terms of either the metallocyclic intermediate 4.36 or a heterogeneous surface reaction mechanism 4.37.



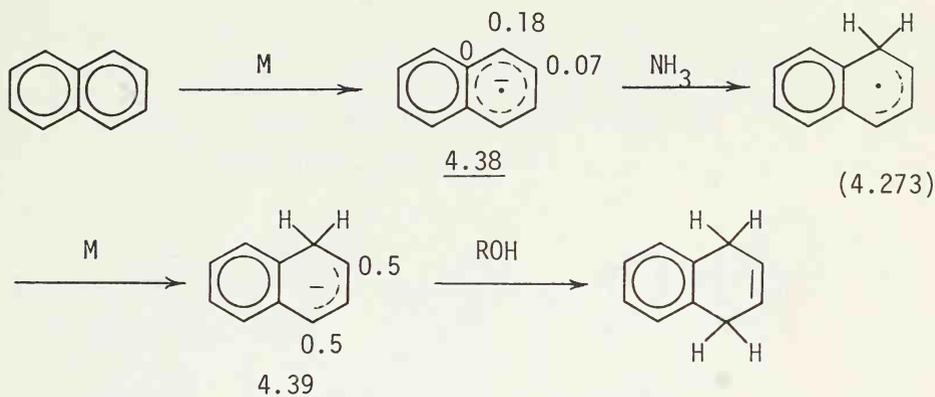
The Birch Reduction. The reduction of arenes with alkali metals is called the Birch reduction (4.482). The reaction provides a unique and synthetically highly useful route to dihydroaromatic derivatives. The reaction typically involves treatment of arenes with lithium or sodium in liquid NH_3 either in the presence or in the absence of an alcohol, such as EtOH and $t\text{-BuOH}$. Lithium has both a higher molar solubility and a higher redox potential in NH_3 than sodium or potassium, and reactions with lithium are often cleaner than those with the heavier alkali metals.

Ease of reduction can be roughly correlated with the reduction potential of the substrate and decreases in the order: anthracene > phenanthrene > naphthalene > biphenyl > benzene. Benzene itself cannot readily be reduced with alkali metals in liquid NH_3 , and its reduction to 1,4-cyclohexadiene requires the use of a more efficient proton donor, such as EtOH . The results can be accommodated by the following scheme (eq. 4.272).



For the reduction of biphenyl and fused polycyclic aromatics, liquid NH_3 is a sufficiently strong acid.

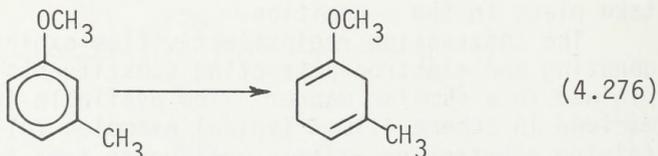
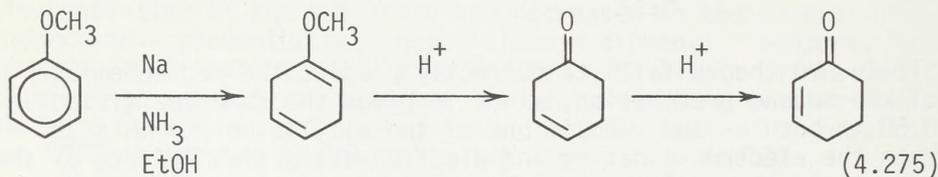
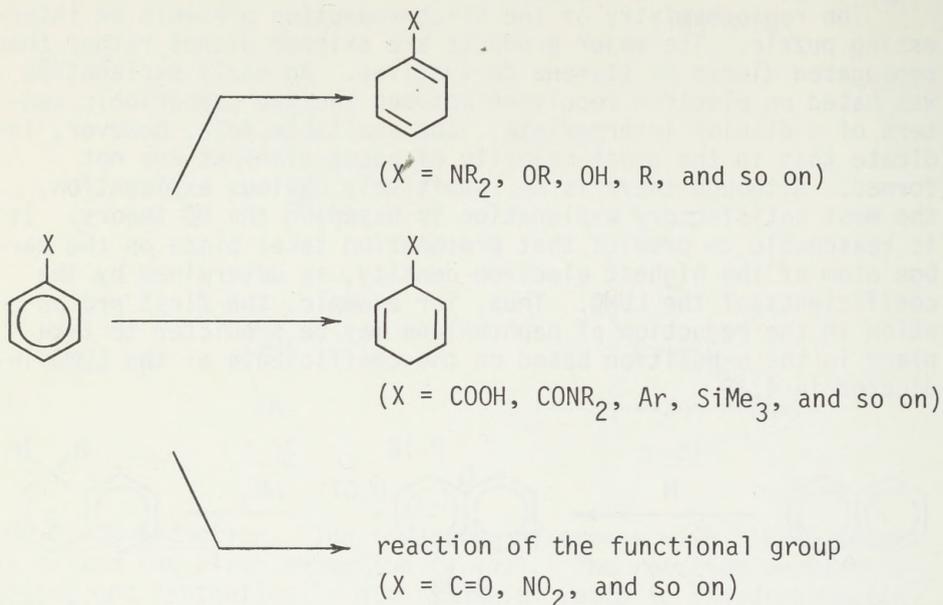
The regiochemistry of the Birch reduction presents an interesting puzzle. The major products are skipped dienes or styrene derivatives. An early explanation was based on electron repulsion between the two carbanionic centers of a dianion intermediate. The available data, however, indicate that in the great majority of cases dianions are not formed. Although there is no intuitively obvious explanation, the most satisfactory explanation is based on the MO theory. It is reasonable to predict that protonation takes place on the carbon atom of the highest electron density, as determined by the coefficients of the LUMO. Thus, for example, the first protonation in the reduction of naphthalene may be predicted to take place in the α -position based on the coefficients of the LUMO indicated in 4.38.



Simple HMO theory fails to correctly predict the regiochemistry of the second protonation, since it gives the same coefficient of 0.50 to both α - and γ -positions of the allylic moiety in 4.39. When the electron-donating and electron-attracting effects of the benzyl and the aryl groups, respectively, are taken into consideration, we can predict that the second protonation will also take place in the α -position.

The contrasting regioselectivities exhibited by electron-donating and electron-attracting substituents can also be explained in a similar manner. The available information is summarized in Scheme 4.10. Typical examples follow. Arenes containing electron-donating substituents tend to give the most highly substituted 1,4-dienes, as shown in eq. 4.276.

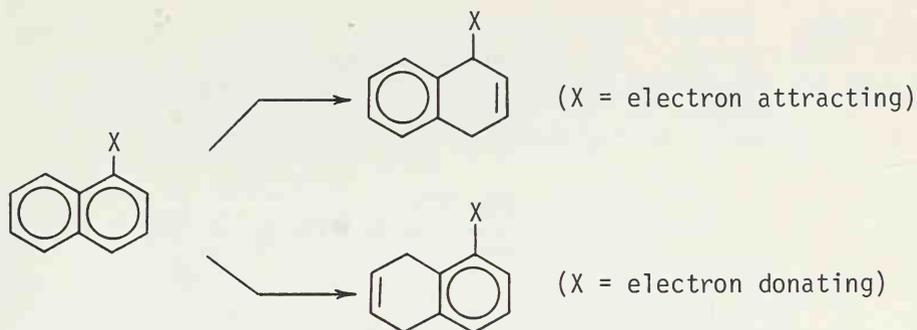
Scheme 4.10



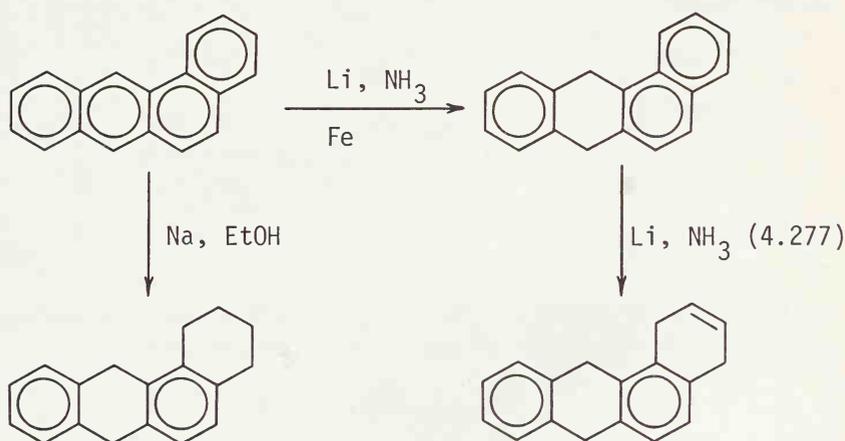
As might be readily expected, electron-attracting groups activate the aromatic ring, while electron-donating groups deactivate it,

as indicated for the cases of naphthalene derivatives in Scheme 4.11.

Scheme 4.11



The course of the Birch reduction can be further controlled in a delicate manner either by varying proton donors or by using suitable additives, as exemplified by the results shown in eq. 4.277 (4.482c).

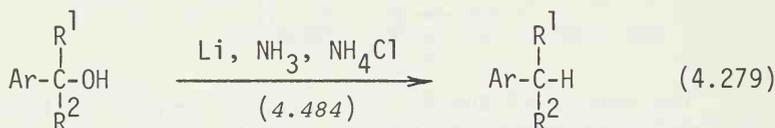


Iron catalyzes the reaction of alkali metals with NH₃ to form metal amides, thereby preventing or minimizing overreduction by excess alkali metals.

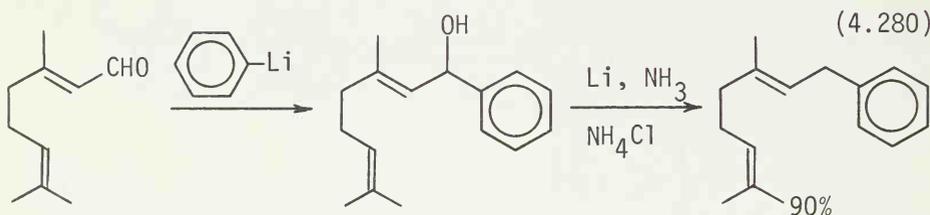
4.4.1.4 Reduction of Carbon-Hetero Atom Single Bonds with Alkali and Alkaline Earth Metals

C-X(halogen) Bonds. The two-step procedure for the reduction of carbon-halogen bonds is discussed in Sect. 4.4.1. β -Chloro enones can be converted into dehalogenated enones with Zn-Ag in MeOH (4.483).

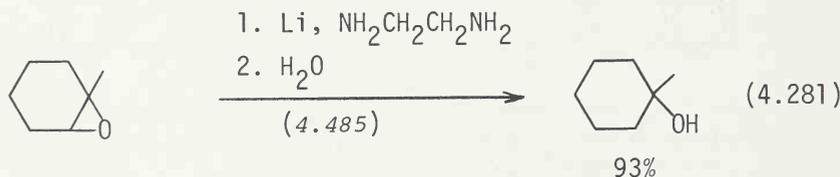
C-O Bonds. Various types of activated C-O bonds can be cleaved with alkali metals. The C-O bonds between benzylic or allylic groups and the oxygen atom as well as those of epoxides are sufficiently reactive so that they do not require an additional activating group, as indicated by eqs. 4.278 to 4.281.



The reaction shown in eq. 4.279 can be used in tandem with the carbonyl addition reactions of organolithiums or Grignard reagents to produce a variety of alkyl-substituted arenes, as shown in eq. 4.280.

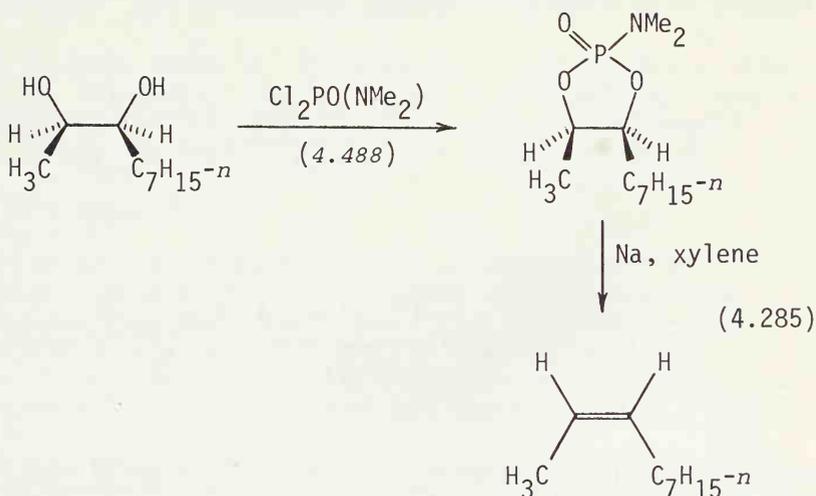
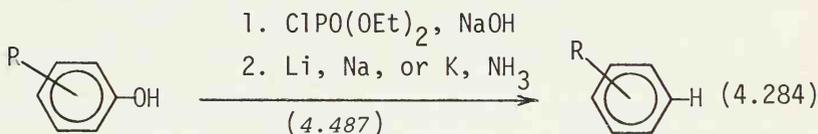
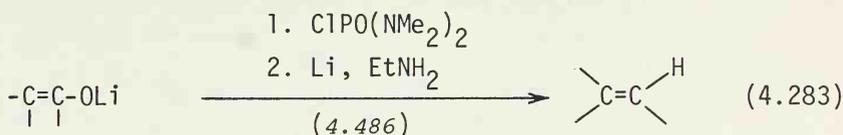
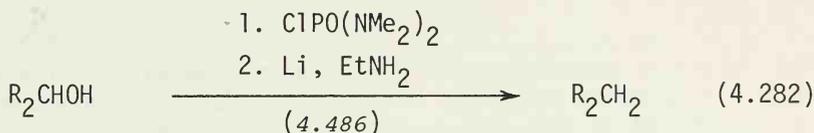


It is noteworthy that neither regiochemical nor stereochemical scrambling takes place to any significant extent.

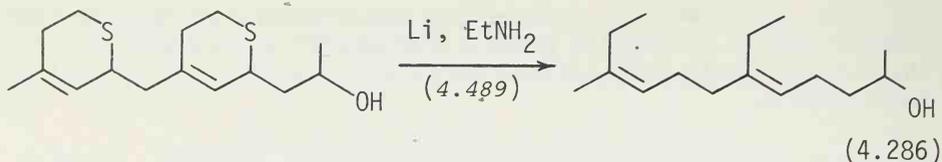


The reaction involves predominant cleavage at the less hindered epoxide carbon atom.

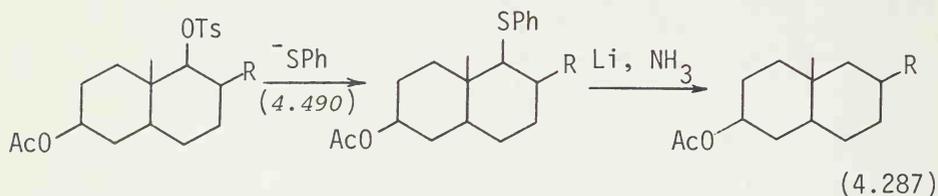
Cleavage of other types of C-O bonds generally requires the presence of an activating group. Phosphoryl groups are some of the most commonly used activating groups, as shown in the following examples.



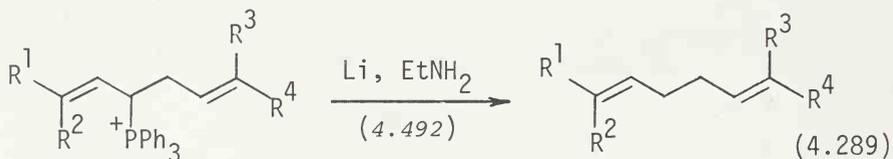
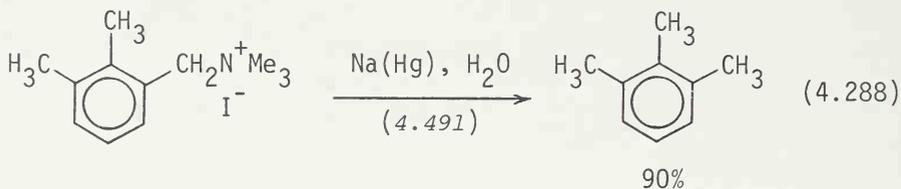
C-S Bonds. Reductive cleavage of the C-S bond with alkali metals is facile and general with respect to the organic group bonded to sulfur. Its scope may be indicated by the following examples.



It should be noted that the cleavage of the allyl-S bonds with lithium in EtNH_2 proceeds in a regio- and stereoselective manner, as mentioned in the discussion of the Biellmann 1,5-diene synthesis (Sect. 4.3.2.1). Even secondary alkyl-S bonds can be cleaved with dissolving metals; see eq. 4.287 (4.490).



C-N and C-P Bonds. Although the C-N and C-P bonds of amines and phosphines are highly resistant to the action of dissolving metals, certain activated ammonium and phosphonium salts can be reduced with dissolving metals, as shown in eqs. 4.288 and 4.289.

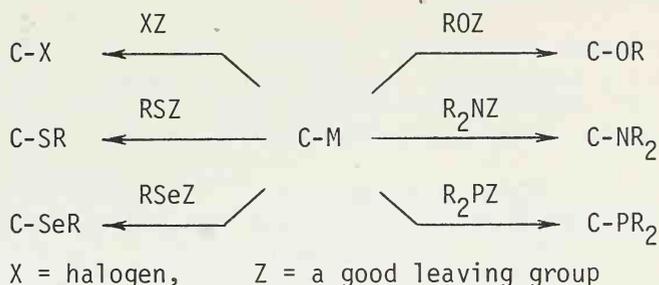


4.4.2 Formation of Other Carbon-Hetero Atom Bonds Containing Nonmetallic Elements

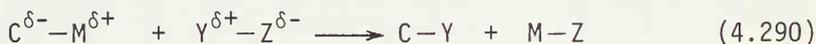
The metal-carbon bond of organometallics of Group IA and Group II metals can be converted into various other carbon-hetero atom

bonds including C-X(halogen), C-O, C-S, C-Se, C-N, and C-P bonds (Scheme 4.12).

Scheme 4.12



These reactions seem to require reagents, represented by Y-Z, which are either highly polarizable or polarized such that the Y and Z groups are partially positively and partially negatively charged, respectively (eq. 4.290). The mechanistic details of these reactions, however, are not very clear. There are indications that some of these reactions proceed by one-electron processes.



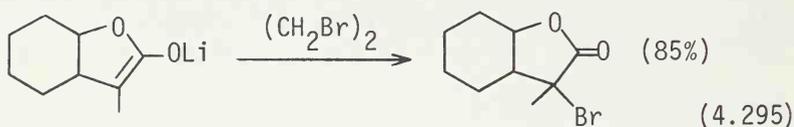
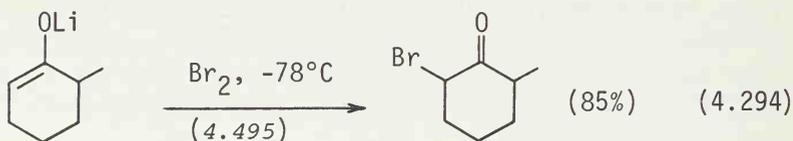
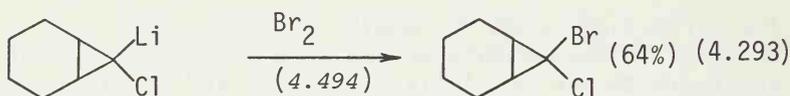
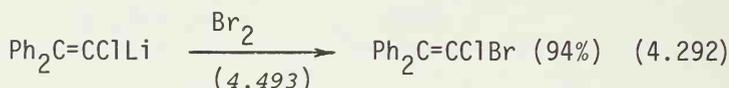
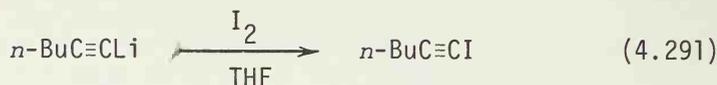
Since the Group V, Group VI, and Group VII elements of our interest, that is, halogens, O, S, Se, N, and P, are generally highly electronegative, the availability of suitable leaving groups Z, which can induce the desired bond polarization, is very limited.

4.4.2.1 Halogenolysis

Conversion of the carbon-metal bond of organometallics of Group IA and Group II metals into carbon-iodine and carbon-bromine bonds is generally a facile process of high synthetic significance. Although less facile, formation of the carbon-chlorine bond is also a synthetically useful reaction. On the other hand, the corresponding fluorination does not appear to be of much synthetic use.

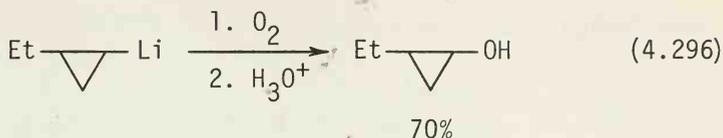
Preferred reagents are molecular halogens, their complexes with phosphines and amines, for example, $\text{Br}_2 \cdot \text{PPh}_3$ and $\text{Br}_2 \cdot \text{pyridine}$, and N-halosuccinimides. The use of complex reagents and N-halosuccinimides is desirable in cases where organometallic intermediates contain some functional groups that are sensitive to molecular halogens, such as olefins.

Halogenolysis of the metal-alkenyl carbon bond can often proceed with retention of configuration. On the other hand, the stereochemical details of the halogenolysis of the metal-alkyl carbon bonds are not very clear. Some representative examples of halogenolysis follow.

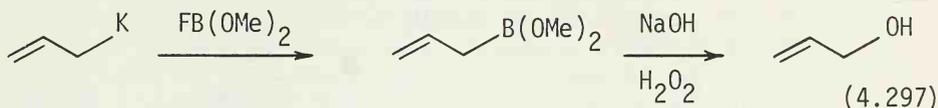


4.4.2.2 Formation of C-O, C-S, C-Se, C-N, and C-P Bonds

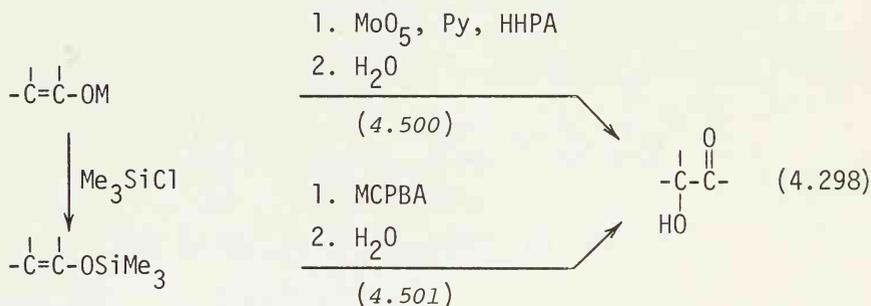
Formation of C-O Bonds. Autoxidation of organoalkali and organoalkaline earth metals can give a variety of products, the major products obtained after hydrolysis being alcohols and coupled hydrocarbons. Autoxidation of Grignard reagents generally gives better yields of alcohols than the corresponding reaction of organolithiums (4.497). Although high yields of alcohols have been obtained in some favorable cases, for example, eq. 4.296 (4.498), these reactions have not yet been developed into synthetically useful procedures.



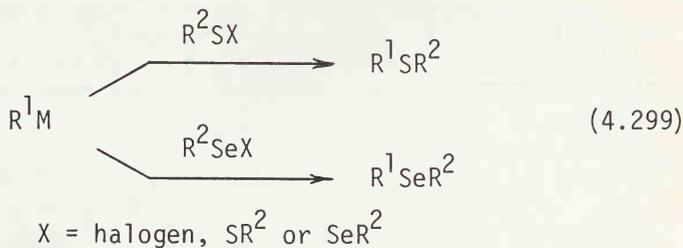
An indirect but more dependable method for converting organometallics of Group IA and Group II metals into alcohols involves their conversion into organodimethoxyboranes followed by oxidation with alkaline hydrogen peroxide; see eq. 4.297 (4.499).



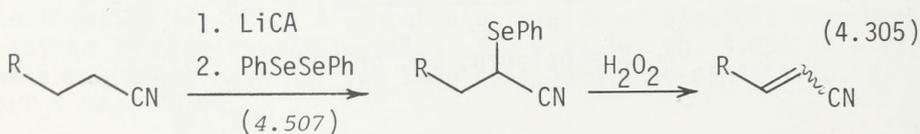
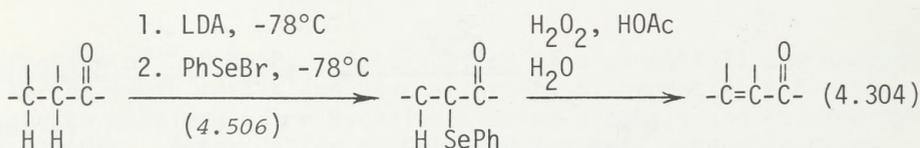
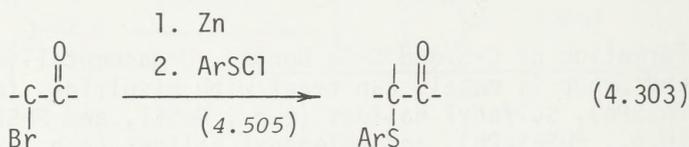
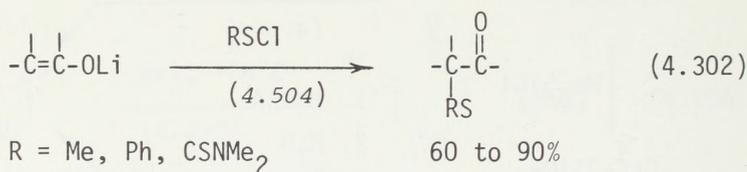
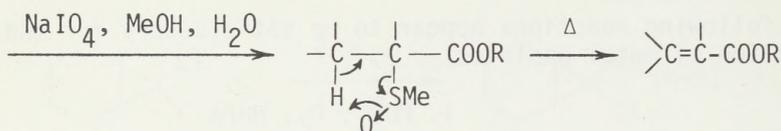
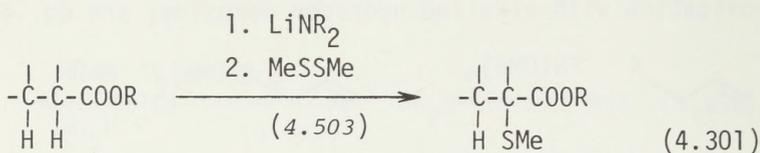
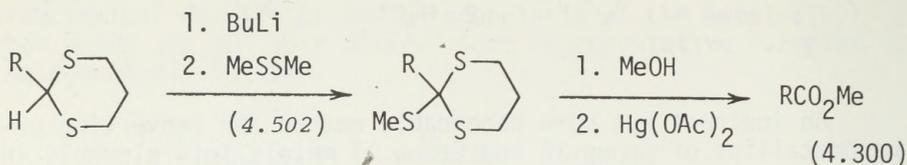
The following reactions appear to be satisfactory for the hydroxylation of metal enolates.

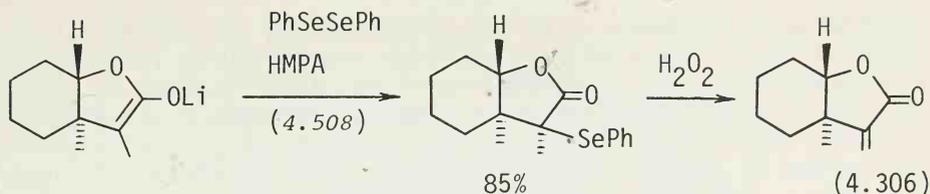


Formation of C-S and C-Se Bonds. Organometallics of Group IA and Group II metals can react with disulfides (e.g., MeSSMe, and PhSSPh), sulfenyl halides (e.g., MeSCl, and PhSCl), diselenides (e.g., PhSeSePh), and selenenyl halides (e.g., PhSeCl) to form the corresponding sulfides and selenides, respectively.

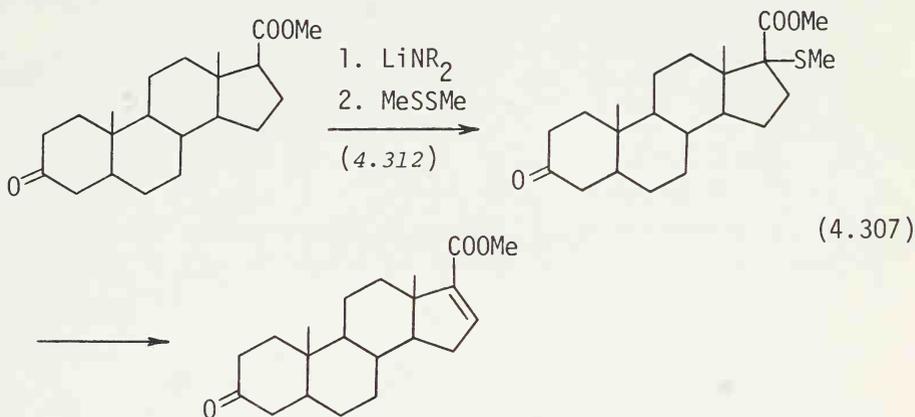


Some typical examples follow.





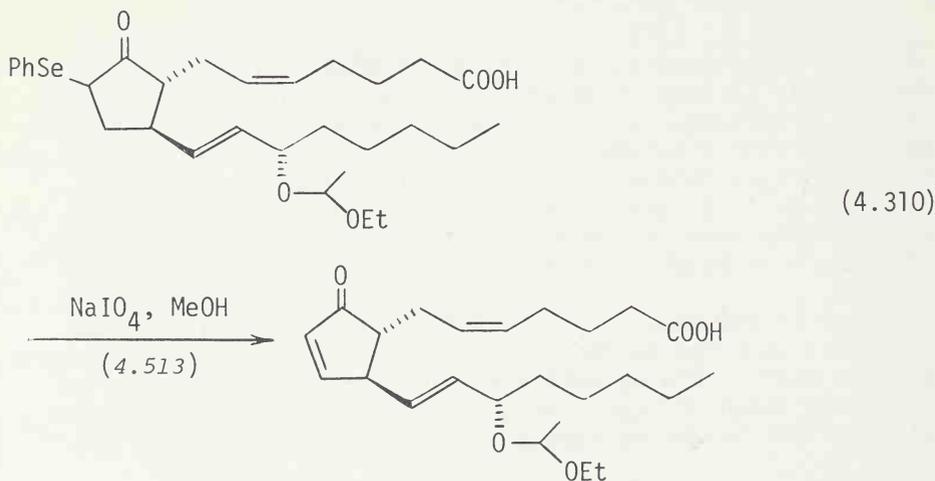
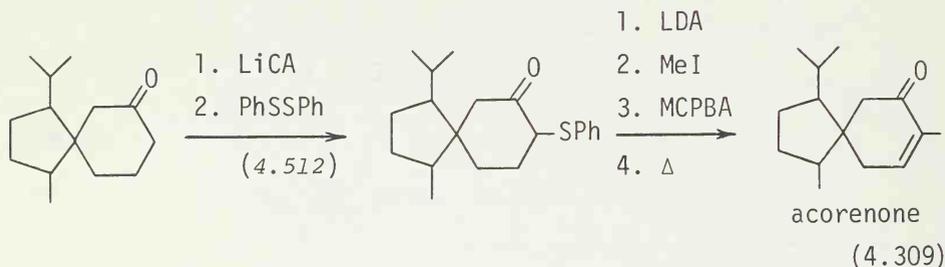
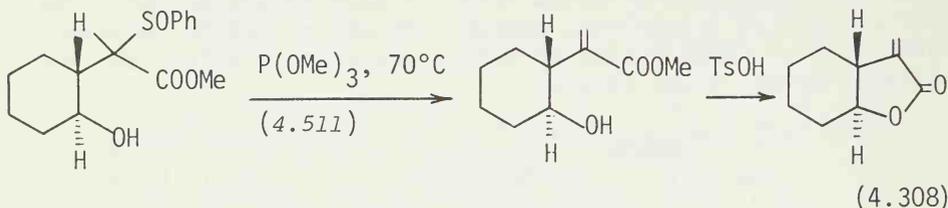
While sulfonyl and selenenyl halides are more reactive than the corresponding disulfides and diselenides, the latter reagents are more convenient. In the sulfonylation, ester or lactone enolates react readily with both MeSSMe and PhSSPh, ketone enolates react only with the more reactive PhSSPh in THF. The use of HMPA as a cosolvent permits the use of MeSSMe, however. The relative reactivities of ketone and ester enolates are indicated by eq. 4.307 (4.312).



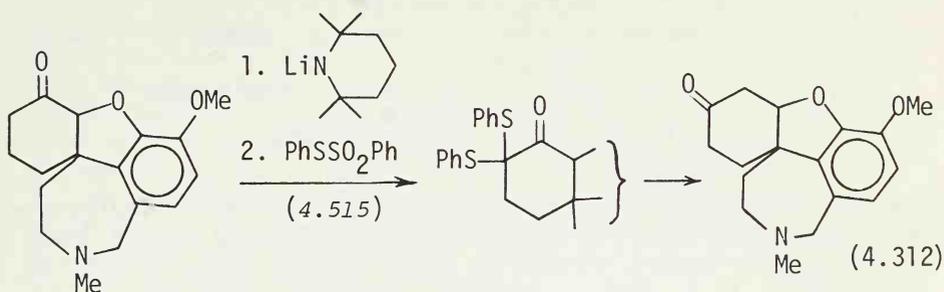
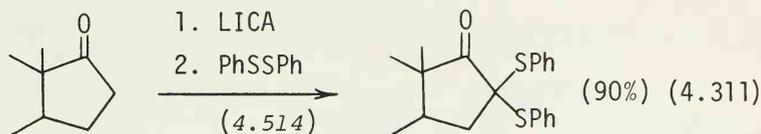
The corresponding selenenylation appears to be much more facile than sulfonylation and can be achieved with PhSeSePh, PhSeCl, or PhSeBr. Although the method does not appear to have been used with aldehyde enolates, it works well with lithium enolates derived from esters (4.509), lactones (4.506, 4.508), nitriles (4.507), and lactams (4.510). Ketone enolates have not successfully been selenenylated with PhSeSePh. Selenenyl halides, such as PhSeCl and PhSeBr, however, are satisfactory (4.506).

One of the major synthetic applications of sulfides and selenides is based on the fact that they can readily be converted into olefins via oxidation-elimination. Conversion of sulfides and selenides into the corresponding oxides is achieved with various oxidizing agents, such as NaIO₄ and H₂O₂. The

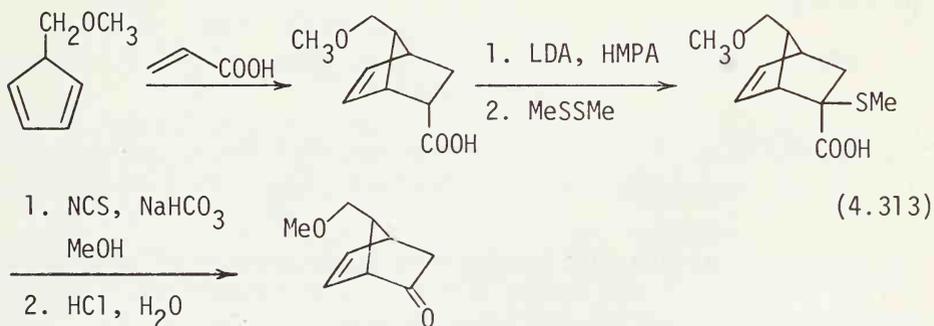
elimination reaction of β -carbonyl-substituted sulfoxides takes place at 25 to 80°C with aryl sulfides and at 110 to 130°C with alkyl sulfides. The corresponding elimination reaction of selenoxides is much more facile and usually takes place at or below room temperature. The regiochemistry of the 2,3-shift of sulfoxides in acyclic systems generally, but not always, follows the order: $C=C-CH_2 \sim C-C-CH_2 > ArCH_2 \sim CH_3 > >C-CH_2 \gg >C-CHR$. The regiochemistry in cyclic systems is controlled to some degree by the cis, syn nature of the 2,3-shift process. The following examples indicate the synthetic utility of the olefination sequence.



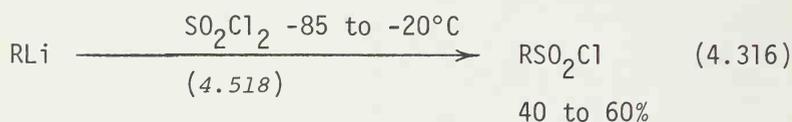
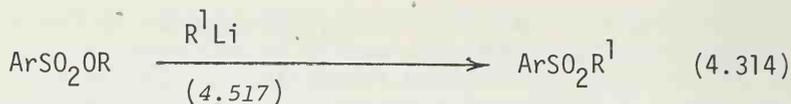
Introduction of two sulfur substituents in the α -position of carbonyl compounds can readily be achieved, as shown in eq. 4.311 (4.514). This bisulfenylation reaction can be adapted to achieve a 1,2-carbonyl transposition, as shown in eq. 4.312 (4.515).



Another useful application of α -sulfenylation of carbonyl compounds is the following oxidative decarboxylation; see eq. 4.313 (4.516).

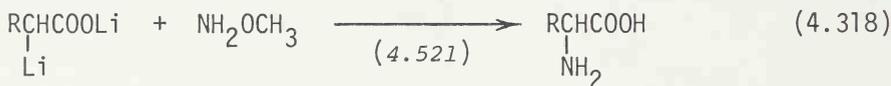
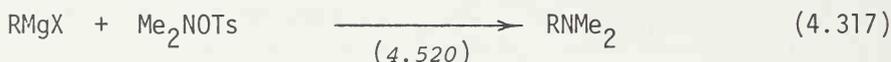


Various other sulfur compounds react with organometallics of Group IA and Group II metals. A few examples are shown below. It is interesting to note that the reaction of sulfonates gives sulfones, whereas that of thiosulfonates gives sulfides.

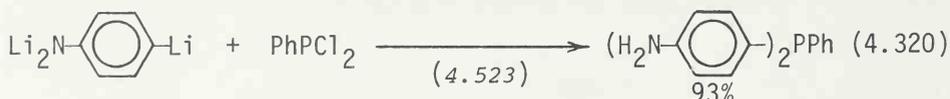
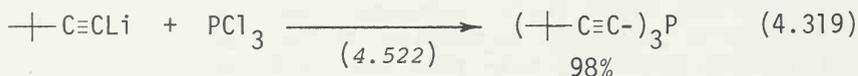


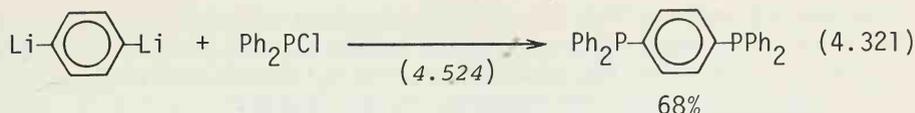
For additional examples and other applications of sulfenylation and selenylation of organometallics of Group IA and Group II metals, see recent reviews by Trost (4.312, 4.519) and Clive (4.290).

Formation of C-N and C-P Bonds. Although conversion of organometallics of Group IA and Group II metals into amines has not been investigated extensively, the following procedure appear promising.



Far more general and straightforward is conversion of organometallics of Group IA and Group II metals into phosphines. A few representative examples are shown below.





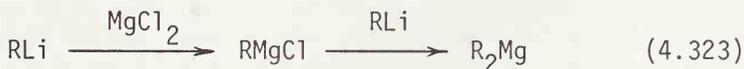
4.4.3 Transmetallation Reactions of Organometallics of Group IA and Group II Metals

As pointed out in Sect. 2.11, the ready availability of organolithiums and Grignard reagents and the high electropositivity of lithium and magnesium make these organometallics highly desirable reagents for the preparation of organometallics containing various other metals. The reaction is also discussed in almost all of the following chapters. For extensive discussions of the reaction, the reader is referred to monographs by Wakefield (4.1), Coates (0.6), and Nesmeyanov (0.8). In this section, a brief survey of the reaction and a few specific examples which are not discussed in other chapters will be presented.

Organolithiums can be and have been converted into organometallics containing essentially all metals except some of Group IA and Group IIA metals (4.1). Although it may seem contradictory to the generalization presented in Sect. 2.11, organolithiums have been used even for the preparation of organosodiums and organopotassiums by making use of the fact that organosodiums and organopotassiums tend to be insoluble in hydrocarbons; see eq. 4.322 (4.525).

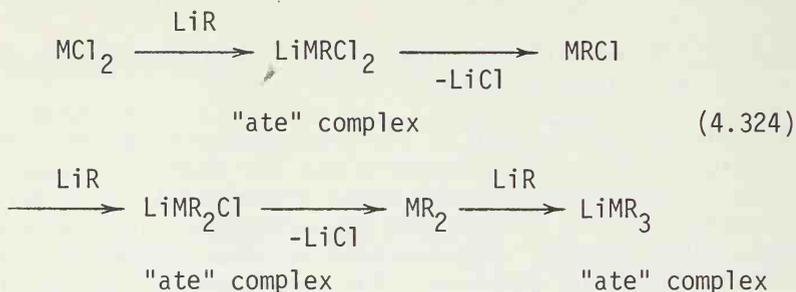


While organolithiums do not appear to have been used in preparing organometallics containing Ca, Sr, and Ba, organoberylliums and organomagnesiums can be prepared from organolithiums (eq. 4.323).



Although the transmetallation reaction of organolithiums and Grignard reagents is of wide applicability and often proceeds cleanly, several side reactions can complicate the desired reaction. Two of the most common side reactions are "ate" complexation and disproportionation. "Ate" complexes are often formed as intermediates in the transmetallation reaction. When they contain a good leaving group, they can decompose under the reac-

tion conditions to form the desired transmetallated products. If not, they are obtained as unwanted products. A general reaction scheme for the reaction between an organolithium and a chloride of a divalent metal, for example, is as follows.



In the reaction shown in eq. 4.324, it might appear that the use of MCl_2 and LiR in the 1:2 ratio would exclusively produce MR_2 . In reality, however, the formation of LiMR_3 is often competitive.

Another very commonly encountered reaction complicating the transmetallation reaction is disproportionation. Except in cases where the overall structure of organometallics is important as in the carbonylation of organoboranes (Sect. 5.2.3.3), for example, the disproportionation reaction does not usually affect the course of an organic synthesis in a serious manner. Thus chemists can successfully use Grignard reagents without knowing the exact Schlenk equilibrium constants.

4.5 OTHER SYNTHETIC APPLICATIONS OF ORGANOMETALLICS OF GROUP IA AND GROUP II METALS

4.5.1 Other Synthetic Applications as Intermediates

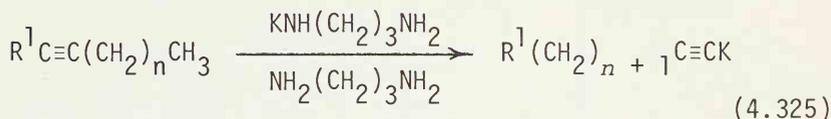
So far we have focused our attention mainly on those synthetic applications of organoalkali and organoalkaline earth metals that involve only the formation and scission of metal-carbon bonds (Type A process in Scheme 3.1). Although much less commonly encountered, those that additionally involve organometallic interconversions (Type B process) can also be synthetically useful. Organometallic interconversion reactions are classified into three types in Sect. 3.2.2.1. Of the three, only those that involve organic ligand transformations accompanied by both formation and cleavage of the metal-carbon bonds (Type III) are worth mentioning here. They include metallotropy, disproportionation

ligand displacement, carbometallation, and ligand migration (Sect. 3.2.2). The synthetic utility of the carbometallation of organoalkali and organoalkaline earth metals is discussed in Sect. 4.3.2.5. Of particular interest here are some metallotropic reactions of organometallics of Group IA and Group II metals.

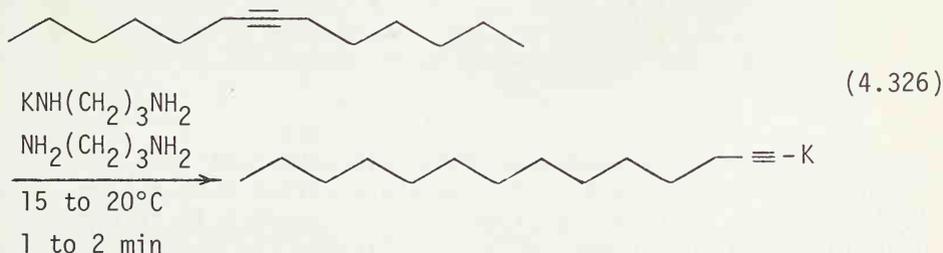
4.5.1.1 Allylic Rearrangement and Acetylene "Zipper"

As pointed out in Sect. 1.6, the 1,3-shift or allylic rearrangement of organometallics is often a very facile process. Although it usually represents a nuisance, it can provide useful synthetic procedures in favorable instances. A few recent discussions of the allylic rearrangement of organomagnesiums are available (4.526 to 4.528).

One of the most interesting and useful functional modification reactions involving organoalkali metals is the acetylene "zipper" reaction which presumably proceeds via a series of allylic (propargyl-allenyl) rearrangements. The reaction involves treatment of internal acetylenes with potassium 3-aminopropylamide (KAPA) in 1,3-diaminopropane (APA), which induces an exceedingly facile multipositional isomerization of the internal acetylenes into terminal acetylenes; see eq. 4.325 (4.325).

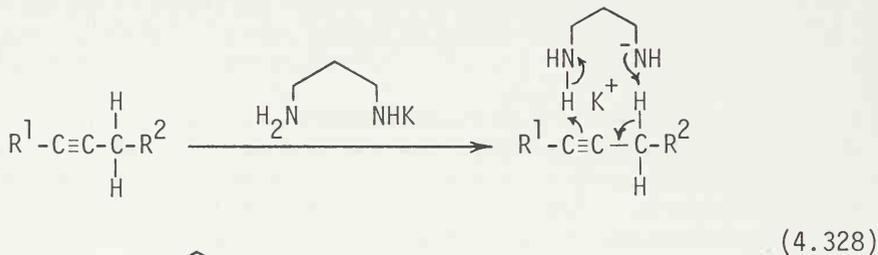
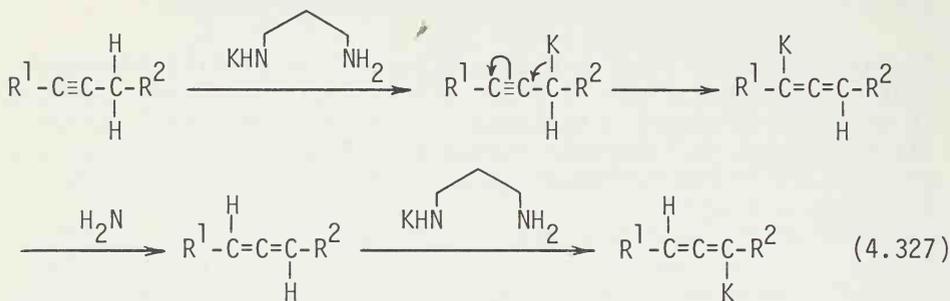


Although many related acetylene isomerization reactions had been reported previously (4.530), the new procedure appears to be far more facile and generally applicable than any of the previously known procedures. Typically, the isomerization of 7-tetradecyne into 1-tetradecyne is over in a few minutes at 15 to 20°C (eq. 4.326).



The product yields are often quantitative in the isomerization of simple acetylenes.

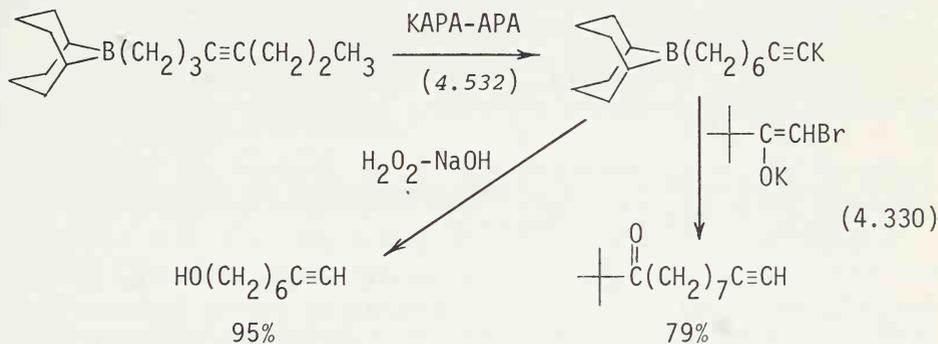
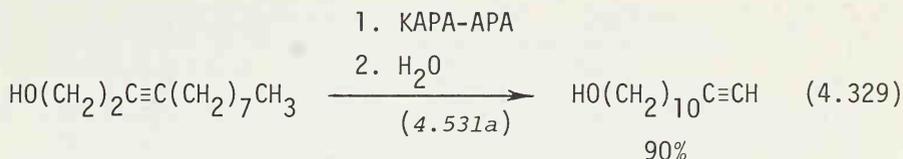
Although the exact course of the reaction is unclear, it can be rationalized in terms of a series of deprotonation-allylic rearrangement-protonation processes, which may be either stepwise (eq. 4.327) or synchronous (eq. 4.328).



Although both schemes are consistent with the fact that isomerization does not proceed past a tertiary carbon center, the latter scheme, proposed by Brown (4.529), appears to be more plausible than the former in that the latter can readily explain the high efficiency of KAPA. Clearly, the major driving force of

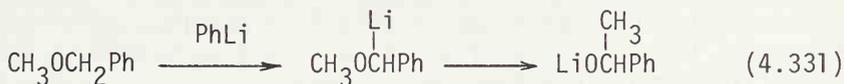
the reaction is provided by the high stability of potassium acetylides formed as the final isomerization product.

Hetero-functional groups tend to interfere with the acetylene "zipper" reaction. The hydroxyl (4.531) and diorganoboryl (4.532) groups which can be readily converted into negatively charged groups, however, are tolerated. As might be expected on the basis of electrostatic repulsion between the carbanionic centers and the negatively charged functional groups, the acetylene isomerization proceeds away from the negatively charged functional groups. A few synthetically useful examples are shown below.

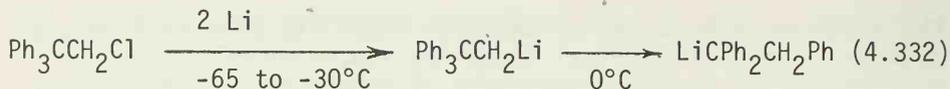


4.5.1.2 Cationotropic 1,2-Shift Reactions

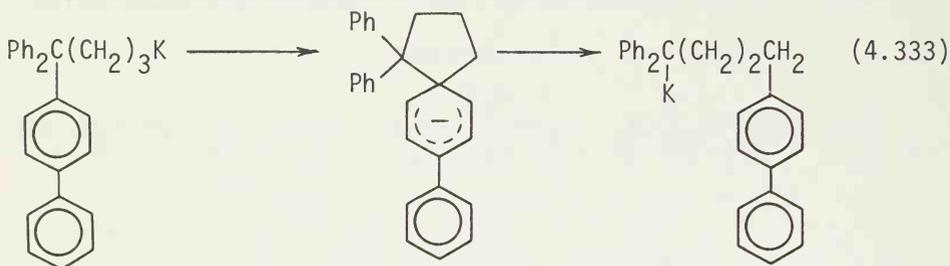
Although cationotropic 1,2-shift reactions are relatively rare, certain types of organoalkali metals undergo such 1,2-shift reactions. The Wittig rearrangement (4.533), for example, eq. 4.331, represents a classic example of this class of reactions.



In the Grovenstein-Zimmerman rearrangement (4.534), an aryl group migrates from a carbon atom to an adjacent carbanionic center as shown in eq. 4.332.



Although no 1,3-shift reaction of this type appears to have been reported, the corresponding 1,4- and 1,5-shift reactions are known. A typical example of the 1,4-migration reaction is shown in eq. 4.333 (4.535).

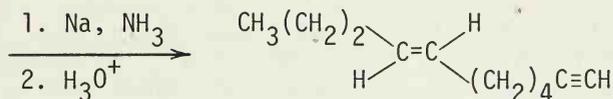
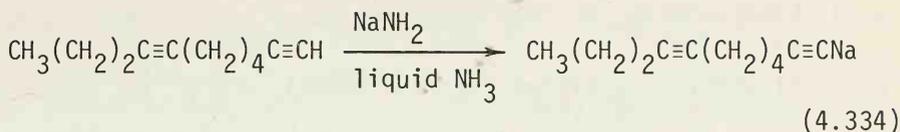


While these organometallic rearrangement reactions are interesting, their synthetic usefulness appears to be rather limited.

4.5.2 Synthetic Utilities of Organometallics of Group IA and Group II Metals as Reagents

One of the most important applications of organometallics of Group IA and Group II metals is their use as strong Brønsted bases. It does not, however, require a detailed discussion here. Although organometallics of Group IA and Group II metals that contain β -hydrogens can act as hydride donors, for example, eq. 3.65, it does not usually represent a synthetically useful application.

In the great majority of cases, conversion of organic compounds into the corresponding organoalkali and organoalkaline earth metals represents activation of the organic compounds. In some cases, however, it can be used to deactivate or protect certain functional groups. For example, conversion of terminal acetylenes into the acetylides of alkali or alkaline earth metals makes the terminal alkynyl group resistant to hydrogenation and dissolving metal reduction (eq. 4.334).



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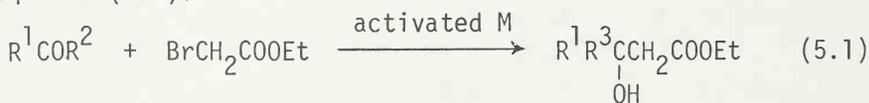
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- 4.530 For a review on earlier results of acetylene isomerization, see Bushby, R. J., *Quart. Rev.*, 24, 585 (1970).
- 4.531 (a) Brown, C. A., and Yamashita, A., *J. C. S. Chem. Comm.*, 959 (1976); (b) Lindhoudt, J. C., van Mourik, G. L., and Pabon, H. J. J., *Tetrahedron Lett.*, 2565 (1976); (c) For an application of this reaction to the synthesis of natural products, see Negishi, E., and Abramovitch, A., *Tetrahedron Lett.*, 411 (1977).
- 4.532 Brown, C. A., and Negishi, E., *J. C. S. Chem. Comm.*, 318 (1977).
- 4.533 Wittig, G., *Angew. Chem.*, 66, 10 (1954).
- 4.534 For a review, see Grovenstein, E., Jr., *Adv. Organometal. Chem.*, 16, 167 (1977).
- 4.535 Grovenstein, E., Jr., and Rhee, J. V., *J. Am. Chem. Soc.*, 97, 769 (1975).

5

ORGANOBORONS AND ORGANOALUMINUMS (B, Al)

5.1 GENERAL CONSIDERATIONS

The Group IIIA elements consist of boron (B, 2.01), aluminum (Al, 1.47), gallium (Ga, 1.82), indium (In, 1.49), and thallium (Tl, 1.44). Their Allred-Rochow electronegativity values are indicated in parentheses. Whereas organometallics of boron and aluminum have found numerous applications in organic synthesis, there have been virtually no synthetically useful reactions of organogalliums and organoindiums. Gallium-containing compounds are far more expensive ($10 \sim 10^3 \times$) than the corresponding compounds containing other Group IIIA elements. Based on cost alone, it seems unlikely that organogallium compounds will find many synthetic applications in the near future. Although not inexpensive, indium-containing compounds are not prohibitively expensive either. Their costs are roughly comparable with those of the corresponding thallium compounds. It is therefore not inconceivable that organoindium compounds might soon find useful synthetic applications in organic synthesis. Indeed, it has recently been shown that the Reformatsky reaction can be carried out with activated indium metal; see Sect. 2.1 (5.1), although the results are inferior to those of the corresponding zinc reaction; see eq. 5.1 (5.2).



286

34 to 55% (M = In)
95 to 98% (M = Zn)

The current limited scope of organoindium chemistry, however, does not permit further discussion of the subject in this book.

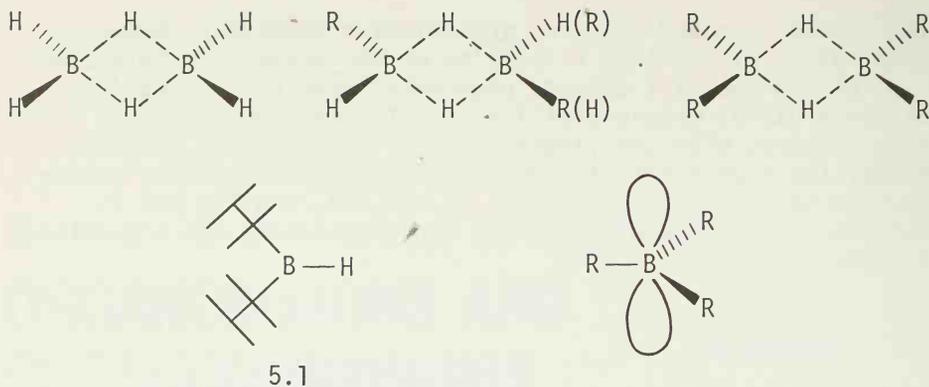
Within the last decade, organothalliums have emerged as uniquely useful organometallics. While thallium compounds share many features with the lighter members of the Group IIIA elements, their chemistry is dominated by certain features unique to some heavy elements, such as Hg, Pb, Pd, and Pt, and is therefore discussed with that of organomercuries and organoleads in Chap. 7.

5.2 ORGANOBORONS

Since 1972 at least four extensive monographs on organoboron chemistry pertinent to organic synthesis have been published (5.3 to 5.6). One by Brown (5.5) entitled *Organic Syntheses via Boranes* is unique in that it contains a number of detailed experimental procedures. There are a few earlier monographs (5.7 to 5.9) and a few more general treatises (0.6, 0.8). Their usefulness, however, is severely limited due to the fact that most of the synthetically interesting reactions, with the notable exception of the hydroboration-oxidation reaction, were developed after their publication.

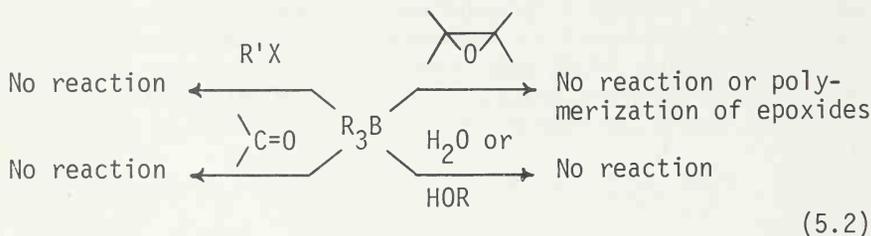
5.2.1 Fundamental Properties of the Boron Atom and Organoboron Compounds

Except for carboranes (5.10) and a very limited number of highly labile subvalent boron compounds, B-X (5.11), organoboron compounds generally exist as either tricoordinate or tetracoordinate species. The trisubstituted derivatives of boron are called *boranes* and exist either as essentially trigonal planar monomeric species or as aggregates in which the boron atoms occupy the central position in an essentially tetrahedral configuration. In fact, nearly all monoorganoboranes (RBH_2) and diorganoboranes (R_2BH), as well as the parent borane (BH_3), exist as dimers, although highly hindered members of diorganoboranes, such as 5.1 may exist as monomers (5.12). On the other hand, triorganoboranes (R_3B) are usually monomeric. For the sake of simplicity, however, organoboranes are often treated as monomers in cases where the degree of aggregation is not a significant factor.



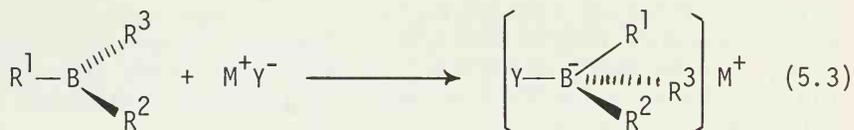
5.2.1.1 Electronegativity and Atomic Size

The electronegativity of boron has been estimated at 2.0, which is relatively close to the value of 2.5 for carbon, and is greater than that of the alkali and alkaline earth metals and of essentially all transition metals which range from 0.86 to 1.75 (Appendix II). According to an empirical equation by Pauling (1.1), the boron-carbon bond may be estimated to be about 90% covalent and only about 10% ionic. It is therefore not surprising that organoboranes generally do not react in the manner of Grignard reagents or organolithium compounds with typical organic and inorganic electrophiles, such as (1) organic halides and sulfonates, (2) various types of carbonyl compounds, (3) epoxides, and (4) water and other "active" hydrogen compounds, under the usual ionic reaction conditions. The relatively short carbon-boron bond length, for example, 1.57 Å for Me_3B , must also be responsible for the highly inaccessible nature of the bonding electrons of the carbon-boron bond in these and other reactions of organoboranes. It should be worth noting, however, that this very property of organoboranes renders them highly tolerant of a variety of electrophilic functional groups.



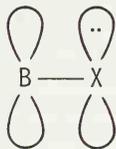
5.2.1.2 Empty p Orbital

The presence and/or ready availability of the empty p orbital makes organoboranes electrophilic or Lewis acidic. Thus organoboranes react readily with a variety of neutral or negatively charged bases to form the corresponding complexes. For example, organoboranes readily form 1:1 complexes with various amines and, in some cases, even with ethers, such as tetrahydrofuran (THF). Similarly, their reaction with a negatively charged species forms the corresponding *organoborates*, for which the monomeric ion pair with the essentially tetrahedral borate anion appears to be a reasonable representation (5.13).

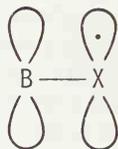


As will become clear, this complexation reaction seems to be one of the crucial steps in essentially all of the ionic reactions of organoboranes.

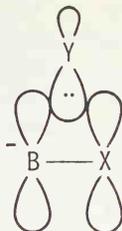
The Lewis acidic property mentioned above is shared by many other organometallics including organoalanes, and is therefore not unique to organoboranes. Far more unique, however, is the ability of the boron p orbital to participate effectively in the $p_\pi-p_\pi$ bonding with the adjacent p or sp^n ($n = 1, 2, \text{ or } 3$) orbitals of other second-row elements, such as C, N, O, and F. This appears to be responsible, at least in part, for the highly unique 1,2-migration reactions and other reactions of organoboron compounds discussed later. Various types of $p_\pi-p_\pi$ interactions pertinent to the present discussion are shown below.



5.2

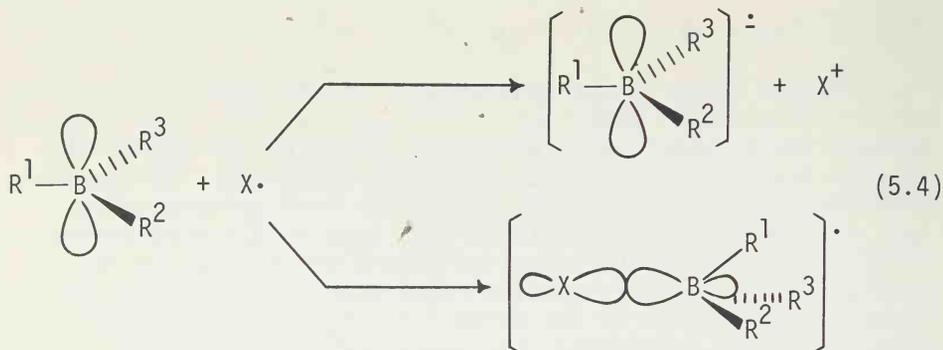


5.3



5.4

The low-lying empty p orbital can also accommodate readily either one electron or a free radical, thereby making organoboranes highly reactive with respect to free-radical reactions.



While quantitative interpretations of the chemistry of organoboron compounds remain difficult, chemists are now in a position to be able to rationalize and, in many cases, even to predict the results on a qualitative basis in terms of a relatively few parameters such as those discussed above.

5.2.2 Preparation of Organoborons

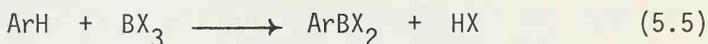
5.2.2.1 Preparation of Organoboranes

Of the twelve general methods for the preparation of organometallics (Chap. 2), only hydrometallation (Method VI), transmetalation (Method XI), heterometallation (Method VII), and metal-hydrogen exchange (Method V) are readily applicable to the preparation of organoboranes with at least some degree of generality. When applicable, hydroboration (5.14) is usually by far the most convenient and is therefore the method of choice. On the other hand, various transmetalation reactions probably represent the most general approach, which has provided various routes to those organoboranes that are not readily accessible via hydroboration. In several significant respects, these two methods complement each other. Since the transmetalation route requires the intermediacy of another organometallic compound, the organoboron compound prepared by this method shares the same limitations and restrictions that the parent organometallic compound encounters. For example, if organolithiums are used as parent species, it is difficult to prepare organoboranes containing electrophilic functional groups. Organoboranes that have stereodefined carbon centers adjacent to the boron atom are also difficult to prepare by this method. On the other hand, a number of such organoboranes have been prepared via hydroboration, as discussed later. In any event, these two by far represent

the most significant methods for the preparation of organoboranes.

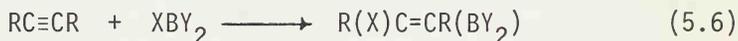
Before discussing the scope and limitations of these methods, however, a brief discussion of other direct and indirect methods is presented below. For further details of this subject, readers are referred to a few recent review articles (5.15, 5.16) and references therein.

Metal-Hydrogen Exchange. Haloboranes can react with arenes to form arylboranes; see eq. 5.5 (2.21, 5.17).

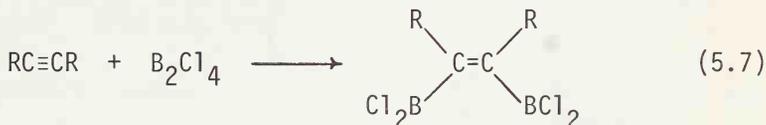


All of the trihaloboranes except BF_3 are useful in this reaction. The reaction can be catalyzed by a number of reagents, such as aluminum, or may be photochemically induced (5.18).

Heterometallation. Haloboranes also react with alkenes and alkynes; see, for example, eq. 5.6 (5.19, 5.20).



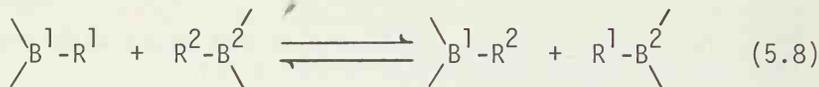
This reaction, however, has not yet been adequately developed for use in organic synthesis. Highly electrophilic diboron compounds of the $\text{X}_2\text{B}-\text{BX}_2$ type add in a cis manner to unsaturated carbon-carbon bonds or cyclopropanes to give 1,2- or 1,3-diboryl compounds; see eq. 5.7 (5.21).



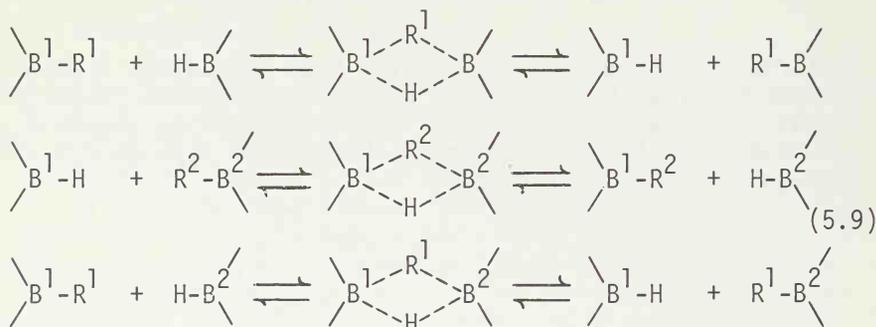
There exist a number of indirect routes to organoboranes. Inasmuch as most of the polar reactions of organoboranes involve transformation of one organoborane into another via 1,2-migration as discussed later in more detail, they represent a number of indirect routes to organoboranes. Then there are various other organoborane interconversion reactions of which (1) disproportionation, (2) isomerization and displacement, and (3) substitution are worth mentioning here. Generally speaking, disproportionation is probably the most facile thermal process that can take place even at 0°C or below. Isomerization and displacement, which presumably involve dehydroboration-rehydroboration, usually become facile only at about 150°C . Substitution

generally requires even higher temperatures, and is significant only above 200°C.

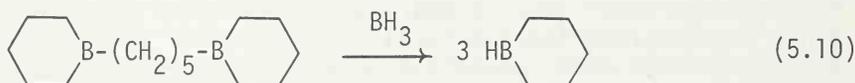
Disproportionation. Although stereochemically quite rigid, organoboranes are generally far more labile than the corresponding carbon compounds and tend to undergo disproportionation, as represented by eq. 5.8.



The reaction is markedly catalyzed by boron hydrides and alanes, and generally proceeds readily even at or below room temperature in the presence of a suitable catalyst. An important consequence is that hydroboration requiring the use of a boron hydride is usually accompanied by disproportionation. Although not yet established, the following four-center mechanism appears consistent with the results obtained with a boron hydride as a catalyst. Consistent with this mechanism is the observation that the disproportionation reaction proceeds with retention of configuration of the organic groups.

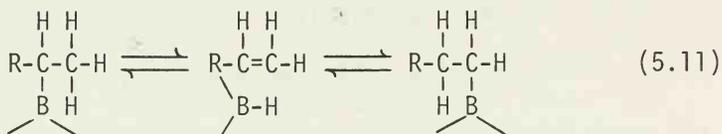


In many cases, disproportionation represents an undesirable side reaction which is to be avoided. In many other cases, however, it can be used as a useful method of preparation, as exemplified in eq. 5.10 (5.22).



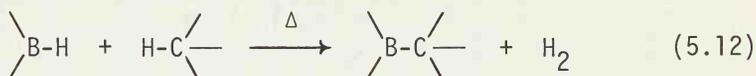
Isomerization and Displacement. At elevated temperatures, generally at about 150°C, organoboranes undergo a facile isomerization that places the boron atom predominantly at the least hindered position of the alkyl groups. The boron atom, however,

will not migrate past a quaternary carbon center. The results are consistent with the following dehydroboration-rehydroboration mechanism; see eq. 5.11 (5.3).



Also consistent with this mechanism is the fact that the presence of another olefin of equal or greater reactivity causes the original olefin to be displaced by the added olefin (5.3).

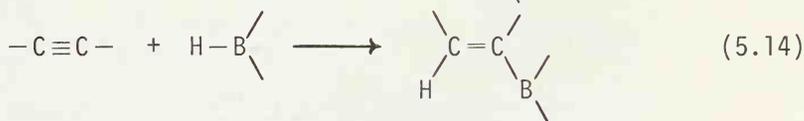
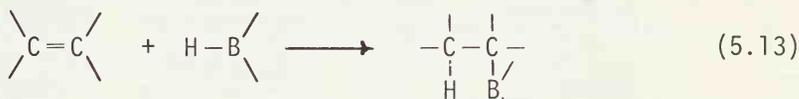
Substitution. The substitution reaction here refers to the irreversible process represented by eq. 5.12.



Usually, the B-H species is generated in situ via dehydroboration at high temperatures. Although the intermolecular substitution reaction has been restricted largely to aromatic hydrocarbons, a number of intramolecular cyclization processes have been observed with aliphatic derivatives (5.23).

5.2.2.2 Hydroboration

Hydroboration involves the addition of the B-H bond to the C=C or C≡C bond (eqs. 5.13 and 5.14).



As mentioned earlier (Sect. 2.6), various other metal hydrides also undergo similar hydrometallation reactions. At the present time, however, hydroboration, discovered by H. C. Brown in 1956 (5.24), is by far the most general and versatile hydrometallation reaction for preparing organometallics as discrete products or intermediates.

Diborane (B_2H_6), which distils at $-92^\circ C$, is most cleanly generated by adding $BF_3 \cdot OEt_2$ to $NaBH_4$ suspended in diglyme. The diborane gas generated is distilled through a couple of dry ice-acetone traps into THF to give the 1:1 complex ($BH_3 \cdot THF$) dissolved in THF (5.5).



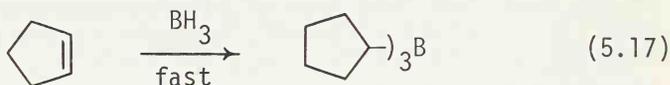
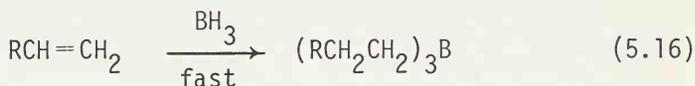
Alternatively, this reaction may be carried out in the presence of olefins and acetylenes in THF or diglyme. Borane-THF is now commercially available. The scope and limitations of the reaction have been well delineated mainly by Brown and his associates, and several excellent reviews are available (5.3 to 5.5, 5.14, 5.25, 5.26).

Scope and Limitations. (1) Except for certain exceedingly hindered olefins virtually all olefins and acetylenes undergo hydroboration with reactive boron hydrides. In this sense, hydroboration seems roughly as general as bromination of these unsaturated compounds. (2) The general reactivity of $BH_3 \cdot THF$ and $BH_3 \cdot SMe_2$ towards typical organic functional groups may be summarized as follows. These organic functional groups are arranged in decreasing order of reactivity.

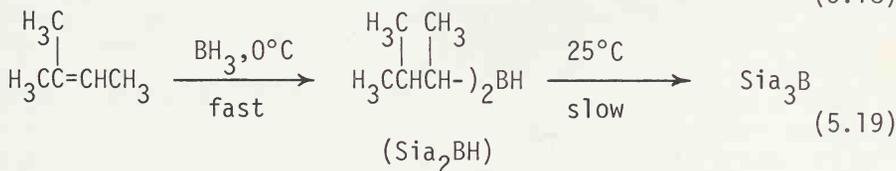
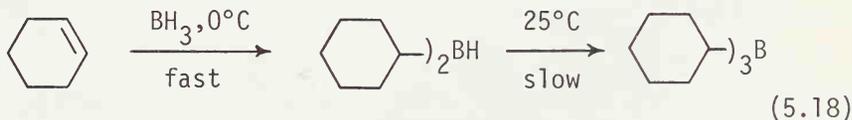
carboxylic acid	$\xrightarrow{\text{very fast}}$	alcohol
olefin and acetylene	$\xrightarrow{\text{fast}}$	organoborane
aldehyde	$\xrightarrow{\text{fast}}$	alcohol
ketones	$\xrightarrow{\text{moderate}}$	alcohol
nitrile	$\xrightarrow{\text{moderate}}$	amine
epoxide	$\xrightarrow{\text{slow}}$	alcohol
ester	$\xrightarrow{\text{slow}}$	alcohol
acyl chloride	$\xrightarrow{\text{very slow}}$	alcohol (?)
nitro	\longrightarrow	No reaction

carboxylic acid salt \longrightarrow No reaction

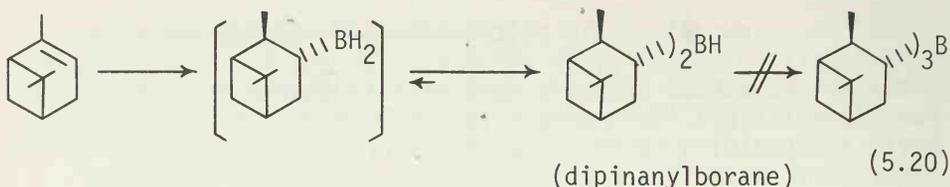
Since hydroboration proceeds more rapidly than most of the other reactions listed, it is generally feasible to prepare organoboranes containing various functional groups such as epoxide, ester, acyl chloride, and nitro groups. Although the cyano group can be accommodated, yields are generally modest. Carboxylic acid, aldehyde, and ketone must generally be protected. (3) No skeletal rearrangement of the organic moiety has been observed. As already mentioned, however, isomerization involving migration of the B-C bond occurs at moderately high temperatures. (4) One of the major limitations is that only certain types of "mixed" organoboranes are readily available. This stems largely from the fact that many types of monoalkylboranes (RBH_2) and dialkylboranes (R_2BH and $\text{R}^1\text{R}^2\text{BH}$) are not readily available as pure substances via hydroboration. The reaction of unhindered olefins (such as ethylene), most of the monosubstituted olefins, and certain disubstituted olefins, with $\text{BH}_3 \cdot \text{THF}$ tends to produce fully alkylated boranes (R_3B) as major products regardless of the reactant ratio used.



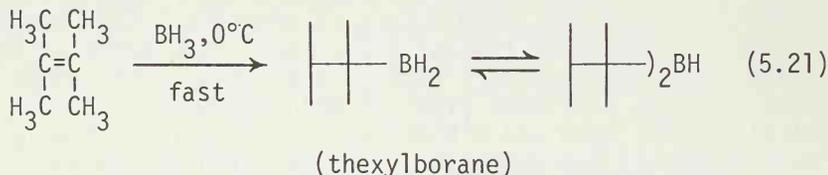
Moderately hindered olefins, such as cyclohexene and 2-methyl-2-butene, tend to produce dialkylboranes, some of which can be prepared cleanly. In many cases the corresponding trialkylboranes can be prepared at or above room temperature.



More highly hindered trisubstituted olefins, however, do not form the corresponding R_3B .



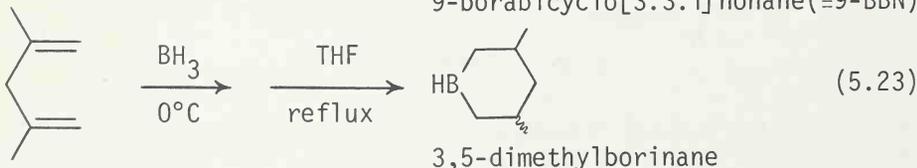
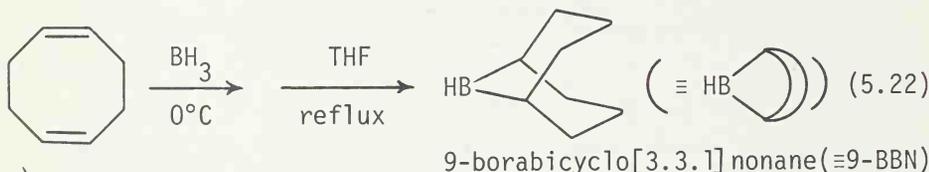
Tetrasubstituted olefins do not generally cleanly form even dialkylboranes, the usual products being monoalkylboranes.



The chemistry of thexylborane has been reviewed comprehensively (5.27). Some of these partially substituted boranes have proven to be valuable reagents, as discussed later.

Mono- and dialkylboranes react with unhindered and moderately hindered olefins to form mixed trialkylboranes of the type $R^1R^2_2B$. Recent development of heterosubstituted hydroborating agents, such as catecholborane (5.28), mono- and dihaloboranes (5.29) have made this type of mixed organoboranes widely available. It is still difficult, however, to prepare totally mixed organoboranes ($R^1R^2R^3B$) except for certain special ones, such as thexyl-dialkylboranes ($\text{---}BR^1R^2$).

Finally, various dienes and trienes have been converted to cyclic organoboranes (5.26). It should be noted that in general, hydroboration has to be followed by disproportionation and/or isomerization for the production of a single cyclic species in high yield. Some of these, most notably 9-BBN, have proved to be valuable reagents.

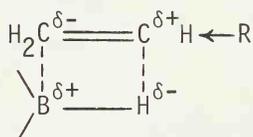


Regiochemistry (Directive Effect). Just as electrophilic aromatic substitution reactions are, hydroboration is influenced by (1) inductive (+I and -I), (2) resonance (+R and -R) and (3) steric (S) effects (IRS effects).

Presumably the B-H bond is polarized with the hydrogen atom having some hydride character. In addition, the boron-containing moiety clearly is sterically more demanding than the hydrogen atom. Some representative results showing the general trend in regiochemistry are summarized below. As a rule, the anti-Markovnikov addition of the B-H bond is observed with simple alkenes (R^1 , R^2 , and R^3 are alkyl groups).

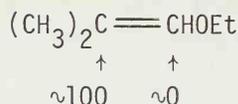
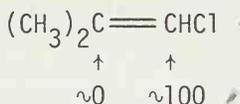
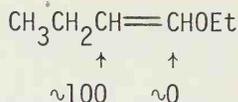
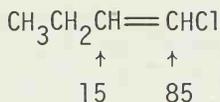
Borane	$\begin{array}{c} \text{H}_2\text{C} \\ \uparrow \\ \text{C} \\ \uparrow \\ \text{CHR}^1 \end{array}$	$\begin{array}{c} \text{H}_2\text{C} \\ \uparrow \\ \text{C} \\ \uparrow \\ \text{CR}^1\text{R}^2 \end{array}$	$\begin{array}{c} \text{R}^1\text{HC} \\ \uparrow \\ \text{C} \\ \uparrow \\ \text{CR}^2\text{R}^3 \end{array}$	Ref.			
$\text{BH}_3 \cdot \text{THF}$	94	6	99	1	98	2	5.14
$\text{ClBH}_2 \cdot \text{OEt}_2$	>99.5	<0.5	>99.9	<0.1	99.7	0.3	5.29
$\begin{array}{c} \\ \\ \text{H}-\text{C}-\text{C}-\text{BH}_2 \\ \\ \text{H} \end{array}$	94 to 95	5 to 6					5.30
Si_2BH	99	1	>99	<1	>99	<1	5.14

These results are readily explained by a combination of inductive (+I) and steric effects exerted by the alkyl substituents.

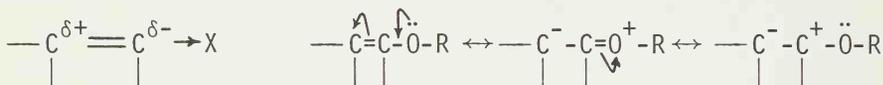


Another point of significance is that the use of either dialkylboranes, such as Si_2BH , or haloboranes, such as $\text{ClBH}_2 \cdot \text{OEt}_2$, is advantageous in controlling the regiochemistry of hydroboration.

Hetero substituents on or near the carbon-carbon double or triple bond can exert strong directive influences. For example, the hydroboration of vinyl halides places the boron atom predominantly on the α -carbon atom, whereas the alkoxy group, which is directly bonded to the olefinic carbon, strongly directs the boron to the β -position (5.31). Some representative results obtained with borane-THF are shown below.

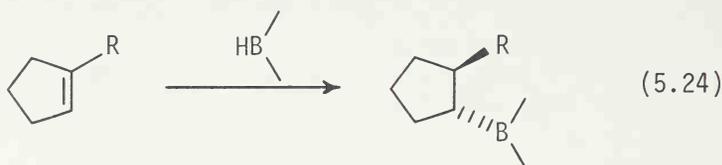


On a qualitative basis, these results are readily interpreted on a reasonable assumption that the -I effect is more significant than the +R effect in the cases of vinyl halides, whereas the hydroboration of enol ethers is totally dominated by the +R effect.

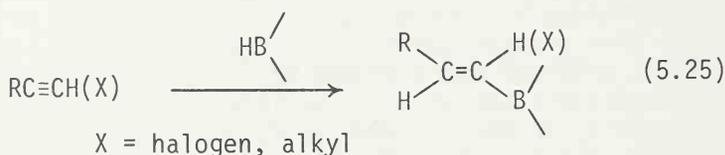


There is little doubt that these IRS effects are also operating in the hydroboration of dienes and polyenes. It has also become evident, however, that some additional effects operate in such cases. Anomalous results are often attributable to the cyclic nature of hydroboration. These results recently have been discussed in detail (5.26).

Stereochemistry. Hydroboration involves an exclusive cis addition of the B-H bond. The ready availability of stereodefined organoboranes shown in eqs. 5.20 and 5.24 makes organoboranes a class of uniquely valuable organometallics.



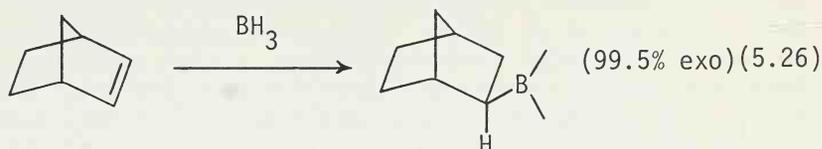
Equally valuable are various stereodefined alkenylboranes readily obtainable from acetylenes (eq. 5.25).



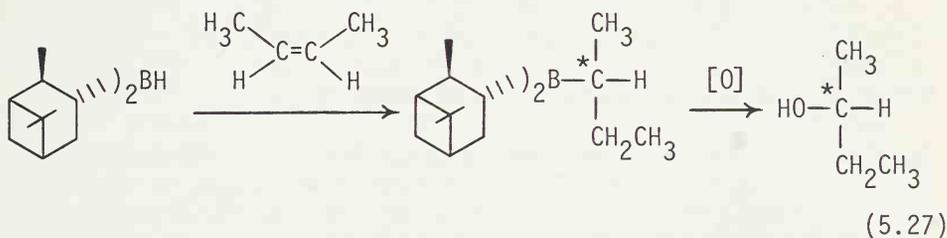
Although various disubstituted boranes, such as dicyclohexylborane, Si_2BH , and catecholborane, as well as certain monosub-

stituted boranes, such as $\text{ClBH}_2 \cdot \text{OEt}_2$, are satisfactory for this transformation, borane-THF and many partially substituted boranes tend to react further with the alkenylboranes to produce gem-dibora derivatives.

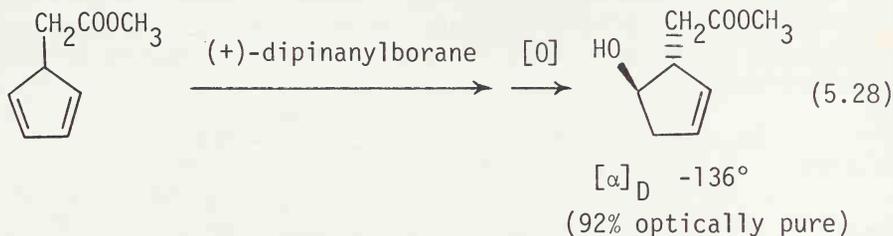
The exclusively *cis* nature of hydroboration provides strong support for the concerted mechanism discussed earlier (Sect. 2.6). When olefins possess two nonequivalent faces, hydroboration takes place predominantly, often nearly exclusively, on the less hindered side.



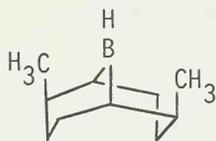
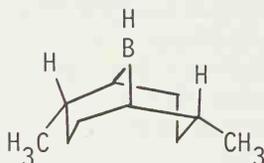
Asymmetric Hydroboration. The reaction of α -pinene with borane takes place nearly exclusively on the less hindered side to give dipinanylborane. If α -pinene is optically pure, an optically pure sample of dipinanylborane with the opposite rotation sign can be obtained (5.32). This reagent permits a remarkably high degree of asymmetric induction (often >90% ee) in its reaction with certain olefins, such as *cis*-2-butene (eq. 5.27).



The following asymmetric synthesis of a prostaglandin intermediate in 92% optical purity demonstrates the synthetic utility of asymmetric hydroboration (5.33).

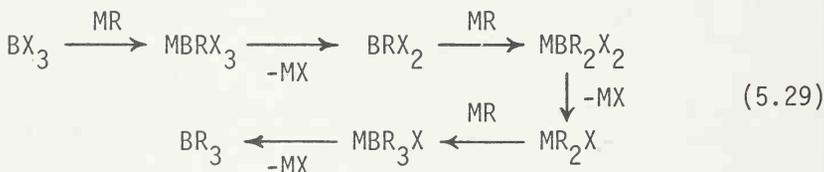


Although highly promising, there exists a serious limitation that must be overcome before the asymmetric hydroboration can become a method of wide applicability. Dipinanylborane, which, as the monomer, is a molecule of C_2 symmetry, is a highly hindered borane and has a tendency to form monopinanylborane (C_1 symmetry) via dehydroboration. The available information indicates that, whereas dipinanylborane is a satisfactory asymmetric hydroboration agent, monopinanylborane is not. Apparently, the C_2 symmetry, which renders both faces of dipinanylborane equivalent, is an essential requirement for a highly satisfactory asymmetric hydroborating agent. Because dehydroboration becomes a serious problem with hindered olefins, satisfactory results have been obtained only with unhindered internal olefins. An ideal asymmetric hydroborating agent would be an optically pure dialkylborane with C_2 symmetry and high stability that can react with a wide range of internal olefins, for example 5.5 or 5.6. The only question is how to make them conveniently.

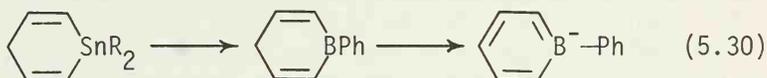
5.55.6

5.2.2.3 Organoboranes via Transmetallation

Despite many unique advantages associated with hydroboration, there are various types of organoboranes that cannot be prepared readily by this method. Such compounds include those organoboranes in which the boron atom is bonded to aryl, *cis*-alkenyl, alkynyl, methyl, neopentyl, and many tertiary alkyl, for example, *t*-butyl, groups. Secondary alkyl groups, which can be derived from internal alkenes bearing two different groups of comparable steric and electronic requirements, present a difficult regiochemical problem. Various transmetallation reactions represented by eq. 5.29 have provided a number of routes to such derivatives.



The scope of the method is too broad to be discussed in detail here (see 0.6, 0.8, 5.6, 5.15). Since the electronegativity of boron is higher than that of most metals, the forward reactions are favorable with various types of organometallics including those of K, Na, Li, Mg, Al, Zn, Cd, and Sn. These metals are arranged more or less in decreasing order of reactivity. Organo-alkali metals and Grignard reagents (5.34) are the most versatile organometallics in this reaction. Organotin, along with other types of organometallics, however, have provided certain unique routes to organoboranes (e.g., 5.35).

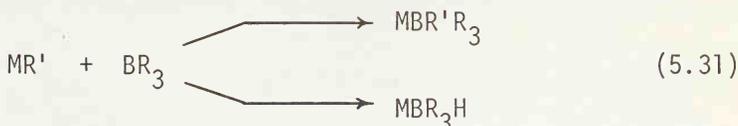


Various groups can be used as the leaving group X (5.6, 5.15). Their relative order of reactivity appears to be: halogen > OR > SR > NR₂. Boron hydrides can also be used (5.6, 5.15). The transmetallation reaction provides a generally satisfactory route to triorganoboranes of the R₃B and R¹R²R³B types. As a method for the preparation of RBX₂ and R₂BX, however, it is only marginally satisfactory. R¹R²BX and R¹R²R³B are not generally obtained in high yields due to extensive disproportionation.

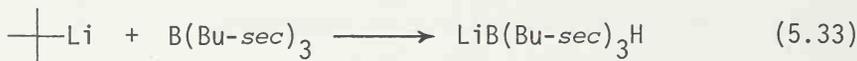
5.2.2.4 Preparation of Organoborates

As shown in the preceding section, organoborates are formed as intermediates in the transmetallation reaction. In this section, we are specifically concerned with thermally stable tetraorganoborates and triorganoborohydrides, two classes of organoboron compounds which have recently exhibited useful synthetic capabilities (5.13, 5.36, 5.37).

Although there are some other routes, the reaction of triorganoboranes with polar organometallics and metal hydrides represents the most general and convenient method by far for the preparation of tetraorganoborates and/or triorganoborohydrides (eqs. 5.31 and 5.32).



These are simple acid-base reactions in which BR_3 acts as a Lewis acid and MR' or MH as a Lewis base. Thus the formation of stable "ate" complexes is favored by the use of strong bases such as those containing K, Na, Li, and Mg. When these organometallics are used, the reactions appear to be quite general. An extensive survey has been made by Negishi (5.38) using organolithiums. The results indicate the following: (1) Thermally stable tetraorganoborates can be obtained from a variety of primary alkylolithiums, aryllithiums, alkenyllithiums, benzylolithiums, and alkynyllithiums. Allyllithium forms relatively weak organoborates in which the two terminal allylic carbons are equivalent by NMR. On the other hand, lithium enolates and cyclopentadienyllithium do not form organoborates under the conditions used. Since sodium cyanide, which is a much weaker base (pK_a 9 to 10) than those mentioned above, forms stable organoborates, the extent of charge delocalization is evidently far more significant as a factor in controlling the stability of organoborates than in controlling the pK_a value. (2) Another significant observation is that, if MR' is sterically demanding and contains one or more β -hydrogens, it tends to form the corresponding triorganoborohydride. This side reaction appears analogous to the reduction reaction frequently observed in the reaction of organolithiums or Grignard reagents with ketones (Sect. 4.3.2.2). As a rule, secondary or tertiary alkylolithiums with β -hydrogens undergo either a predominant or an exclusive borohydride formation even with moderately hindered triorganoboranes (5.38). This side reaction, however, has provided one of the most general routes to triorganoborohydrides (5.39), as exemplified by eq. 5.33.



The reaction of triorganoboranes with metal hydrides, such as LiH and KH , represents another general route to triorganoborohydrides; see eq. 5.32 (5.40). The reaction of LiH , however, is sluggish when organoboranes are hindered. The use of KH , which is far more reactive than LiH , is advantageous in such cases (5.41).

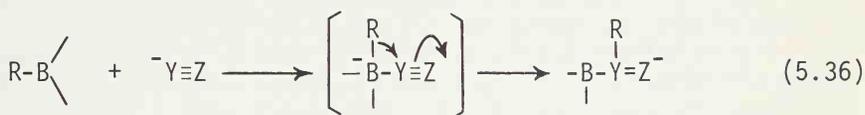
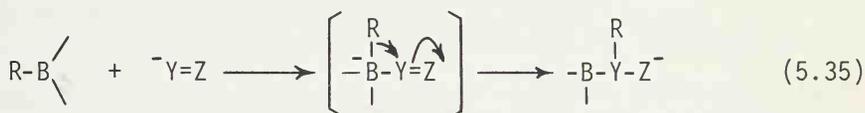
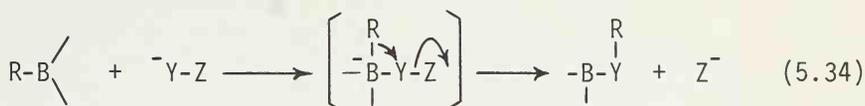
5.2.3. Reactions of Organoborons

5.2.3.1 General Reaction Patterns

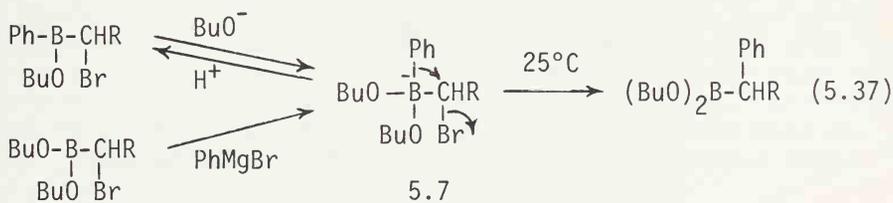
Only in a relatively few cases have the mechanisms of organoboron reactions been fully established. Nevertheless, it is use-

ful to attempt to summarize and classify various organoboron reactions based on the available data including the reactant-product relations.

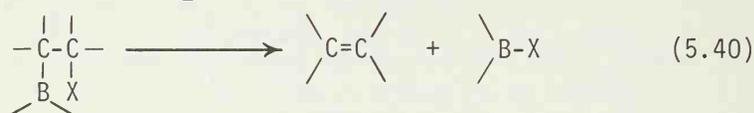
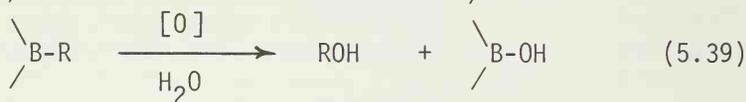
Ionic Reactions. The weakly nucleophilic but highly electrophilic nature of organoboranes has already been mentioned. The organoborates formed by the reaction of organoboranes with basic or nucleophilic species are often thermally stable and do not undergo any further spontaneous reactions in such cases. When the nucleophile is appropriately substituted, however, the 1,2-migration reactions represented by the following general equations take place.



The key features common to all of these reactions are the formation of the borate anion as a transient species and the intramolecular 1,2-migration. Various minor variations of these mechanistic pathways, such as stepwise analogs and vinyls, are also conceivable. It is important to note that the great majority of ionic reactions of organoboranes discovered and developed by H. C. Brown and others (5.3 to 5.6) can be rationalized in terms of these mechanistic pathways. Although there is little doubt about the intermediacy of the appropriately substituted organoborates, it has seldom been established. At least in one case, however, Matteson and Mah (5.42) have clearly established the intermediacy of an α -bromoorganoborate (5.7) as summarized in eq. 5.37.



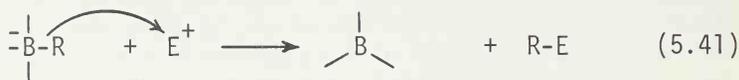
The products of 1,2-migration reactions are new organoboranes which must be further converted into the desired organic compounds. This is accomplished in most cases by one of three methods: (1) protonolysis (eq. 5.38), (2) oxidation (eq. 5.39), and (3) elimination (eq. 5.40).



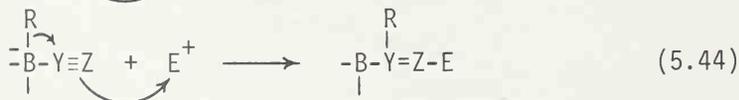
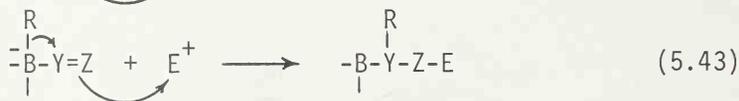
These reactions are discussed later in more detail.

Ionic Reactions of Stable Organoborates. We have so far dealt with the ionic reactions of organoboranes which presumably go through unstable organoborates (eqs. 5.34 to 5.36). It has recently been recognized that thermally stable organoborate anions, which are negatively charged and coordinatively saturated, act as unique nucleophiles (5.13). They react with a variety of organic and inorganic electrophiles via either intermolecular or intramolecular transfer, as represented by eqs. 5.41 to 5.44.

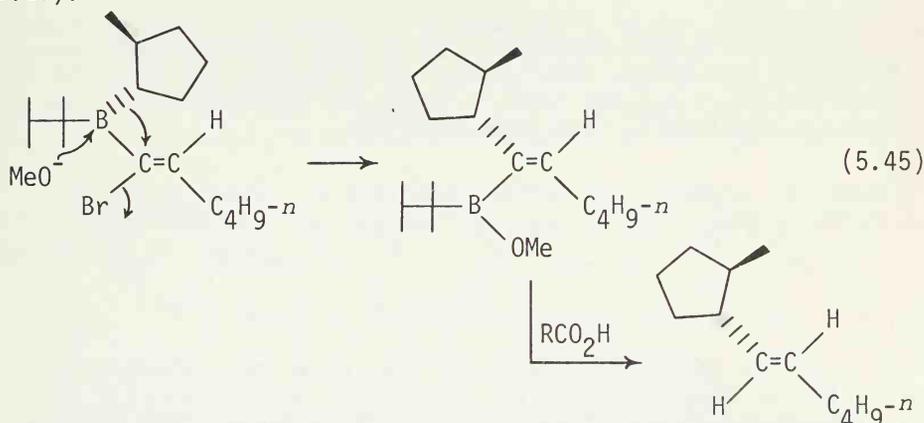
Intermolecular transfer:



Intramolecular transfer:

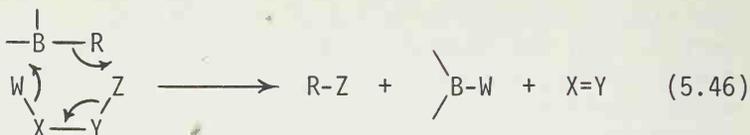


In the intermolecular transfer reaction the organoborate acts as the boron version of a Grignard-like reagent with very mild reactivity. On the other hand, the intramolecular transfer reactions are closely related to those of organoboranes. The only difference is that the organoborate reactions require activation by electrophiles, whereas the organoborane reactions generally occur spontaneously. It should also be emphasized that these intramolecular transfer reactions are not only highly unique as organometallic reactions, but tend to take place much more readily than the intermolecular reactions in cases where both can occur. These reactions may be best interpreted within the framework of the well-known anionotropic 1,2-migration reactions, such as the Wagner-Meerwein rearrangement. Significantly, the intramolecular transfer reactions of both organoboranes and organoborates have proceeded with retention of configuration of the migrating group. Mechanistic considerations also predict inversion of configuration at the migration terminus, which has been borne out in some cases; see eq. 5.45, for example (5.43 to 5.45).

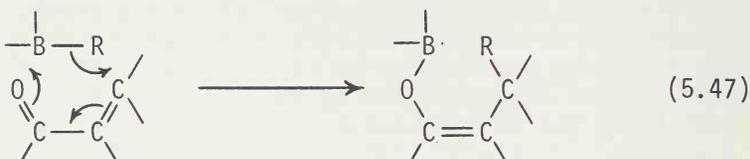


Concerted Reactions. Considering the relatively covalent nature of the B-C bond and the size of the boron atom and its valence shell orbitals, which are comparable to those of the carbon atom, organoborons might be expected to participate readily in some concerted pericyclic reactions. The information available strongly indicates that the protonolysis of organoboranes with carboxylic acids is best viewed as a concerted $[2_s + 4_s]$ reaction in which the boranes act as 2-electron components. Although relatively few other reactions of this type have been observed, there exists a strong possibility that additional reac-

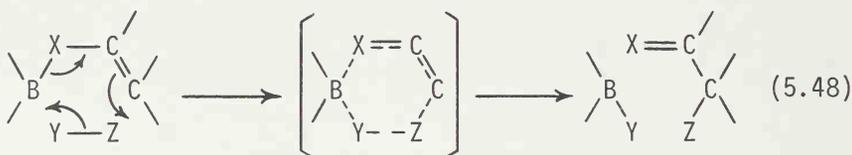
tions, which may be represented by eq. 5.46 or its modifications, may be found in the future.



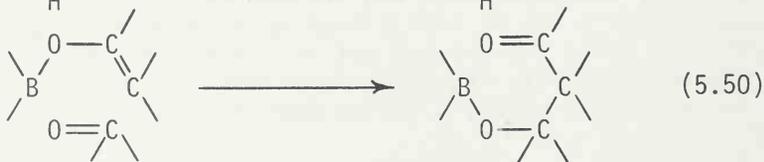
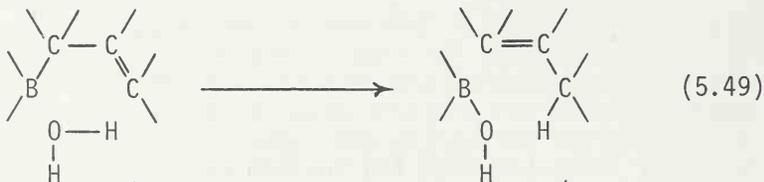
In fact, a recent study on the conjugate addition reaction of organoboranes (5.46) suggests that, at least in some cases, the reaction may proceed by a nonfree-radical mechanism. The following concerted mechanism appears plausible.

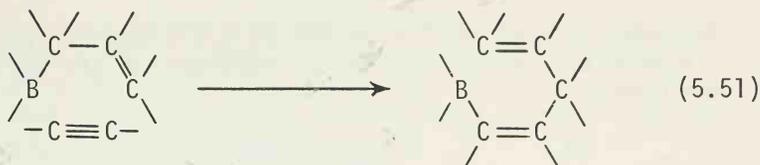


Within the last decade or two, a considerable number of organoborane reactions, which appear to be best represented by the concerted $[4_s + 2_s]$ reaction in which the boranes act as four-electron components, have been observed.

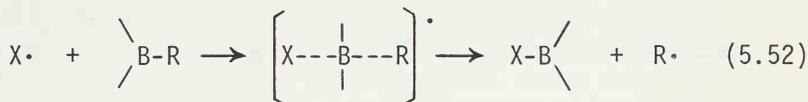


Although the examples observed to date have been essentially restricted to some reactions of (1) allylic boranes and (2) alkenyloxyboranes (eqs. 5.49 to 5.51), it is likely that the general scheme will represent many other unknown reactions.



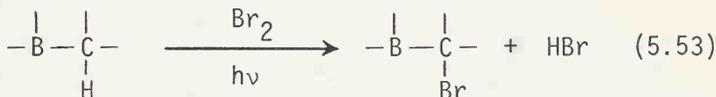


Free-Radical Reactions. Recently it has been established that organoboranes readily participate in at least two distinctly different free-radical reactions. Although there has been essentially no firmly established example of the bimolecular homolytic substitution (s_{H^2}) taking place at a simple saturated carbon center, organoboranes readily participate in this reaction, which may be represented by eq. 5.52 (5.47).

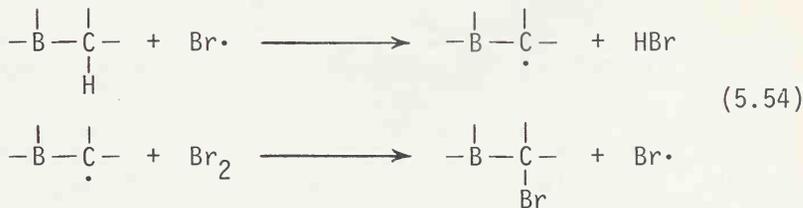


Once an organic free radical is generated, it can participate in various free-radical reactions, as discussed later in detail. It should be pointed out that the s_{H^2} reaction is not unique to organoboranes and that a number of other metals, such as Li, Mg, Zn, Cd, Al, and Tl, have also participated in the s_{H^2} reaction (5.47).

Far more unique to organoborons is the α -abstraction reaction exemplified by the bromination reaction of organoboranes; see eq. 5.53 (5.48).

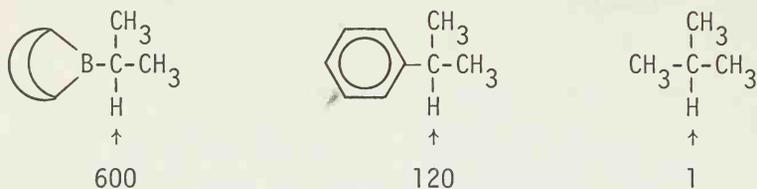


The available data support the following free-radical chain mechanism (5.49).



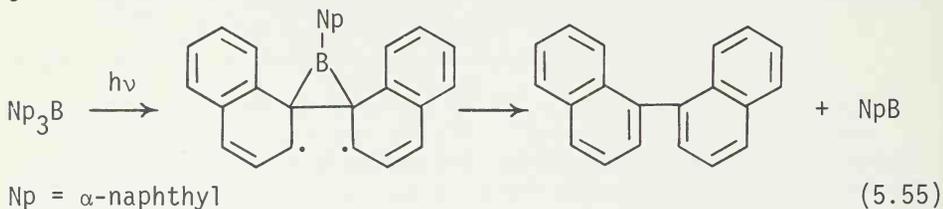
The $p_{\pi}-p_{\pi}$ interaction discussed earlier (5.3) must be responsible for promoting this reaction. A more recent study suggests

that the α -C-H of B-alkyl-9-BBN is 5.5 times as reactive as that of cumene and some 600 times as reactive as the tertiary C-H of isobutane (5.49).



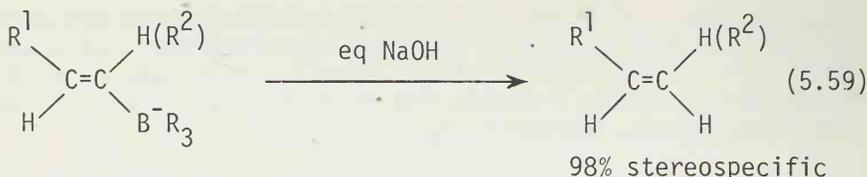
What are the factors controlling the point of attack by a free radical? Although this question has not been fully solved, nitrogen and oxygen free radicals have participated mainly in the s_H2 reaction, whereas the bromine free radical undergoes the α -abstraction. Based on these observations, we may tentatively conclude that those free radicals that can form thermodynamically highly stable bonds to boron, such as the B-O and B-N bonds, prefer the s_H2 reaction. With others the α -abstraction can be a dominant course of the reaction.

There can be a variety of other free-radical reactions for organoboron compounds. For example, the following photochemical reaction of trinaphthylborane has been interpreted in terms of the boron di- π -methane free-radical reaction (5.11). At present, however, the s_H2 reaction and the α -abstraction reaction represent the great majority of the free-radical reactions of organoboranes.



5.2.3.2 Formation of Carbon-Hetero Atom Bonds via Organoborons

Organoboron compounds can be converted into various organic compounds containing C-H, C-O, C-X (X = halogen), C-N, and C-S bonds. Virtually nothing is known about the formation of the C-P bond via cleavage of the C-B bond. Organoboron compounds can serve as precursors of other organometallic compounds.



expected, the basic hydrolysis of the alkynyl-boron bond of either organoboranes or organoborates is very facile. The allyl-boron bond can be cleaved readily even with water, presumably via the unique six-center mechanism shown in eq. 5.49. The reactions of organoborons with various proton donors are summarized in Table 5.1.

Table 5.1 Protonolysis of Organoborons

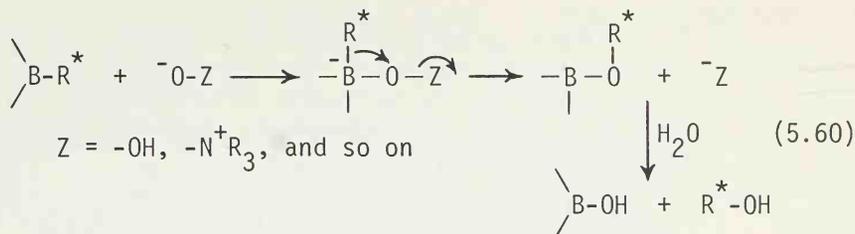
Reagent	Organoborons	
	Organoboranes	Organoborates
Acids	Protonolysis with carboxylic acids ^a	Facile protonolysis or 1,2-migration
Bases (aqueous)	Stable ^a	Cleavage of unsaturated groups

^aEase of protonolysis varies. Alkynyl and allyl groups are cleaved under either condition.

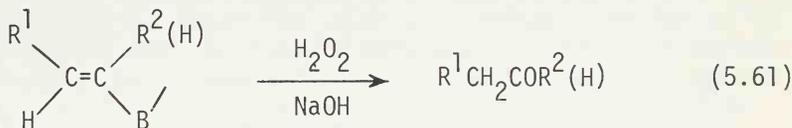
Hydrogenolysis. The B-C bond is quite stable to hydrogenolysis. Since the hydrogenolysis reaction has been carried out at elevated temperatures, it is not clear if the reaction involves direct cleavage of the B-C bond with hydrogen or dehydroboration-hydrogenation (5.51).

Oxidation. Organoboranes are readily oxidized by a variety of reagents. The presence of an empty *p* orbital and the high thermodynamic stability of the B-O bond (115 to 135 kcal/mole) must be responsible for the ease of oxidation.

(a) Oxidation with alkaline hydrogen peroxide and tertiary amine N-oxides. The oxidation of organoboranes with 30% hydrogen peroxide and a suitable base, such as NaOH, NaOAc, or the $\text{NaH}_2\text{PO}_4\text{-K}_2\text{HPO}_4$ buffer solution, is by far the most dependable and convenient laboratory method (5.3 to 5.6). This reaction as well as the reaction with amine N-oxides is believed to proceed as shown in eq. 5.60 (5.52).



Essentially all types of organoboranes can be converted into the corresponding alcohols with retention of configuration. Alkenylboranes are converted into ketones and aldehydes (eq. 5.61), and arylboranes into phenols; see eq. 5.62 (5.53). Under aqueous conditions, however, the alkynyl-boron bond undergoes protonolysis preferentially.

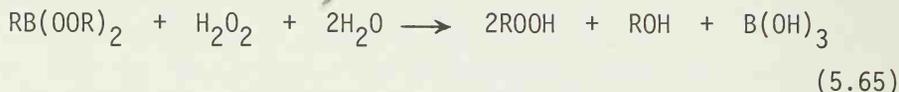


As might be expected based on the mechanism shown in eq. 5.60, the coordinatively saturated organoborates are not oxidized until they are converted into organoboranes via protonolysis or via some other reactions. Thus, for example, only three of the four alkyl groups (R) of LiBR_4 can be converted into alcohols.

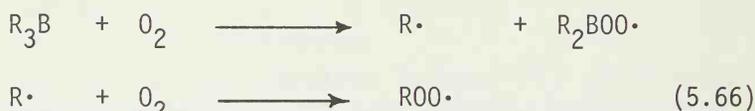
(b) Other oxidation reactions. Organoboranes can be directly converted into ketones by oxidation with chromic acids (5.54). The reaction of organoboranes with oxygen involves an S_H2 reaction (5.47). The initial product is a peroxide; see eq. 5.63 (5.55), which reacts further with a second mole of oxygen to form a diperoxide (eq. 5.64).



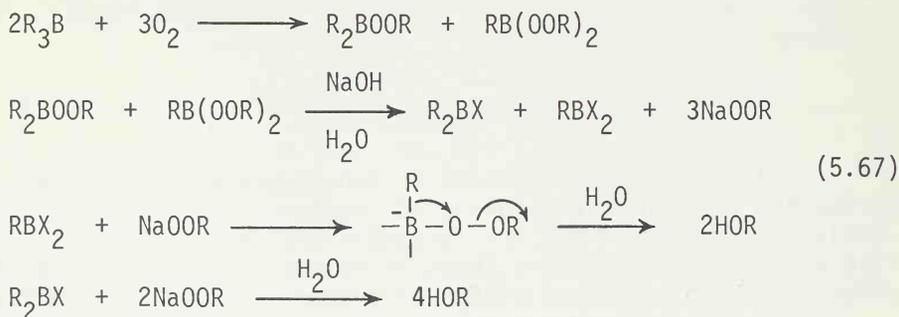
Addition of 30% H_2O_2 liberates the alkyl hydroperoxide; see eq. 5.65 (5.56).



A free-radical chain mechanism involving an S_H2 reaction is consistent with the results (eq. 5.66) (5.57).

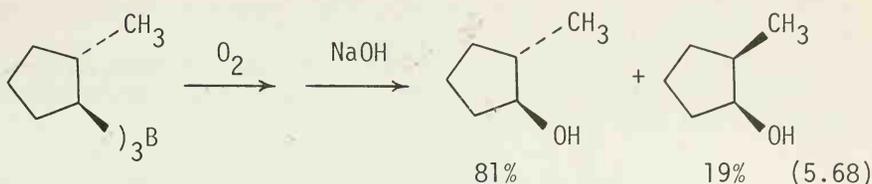


When a trialkylborane is reacted with 1.5 molar equivalents of oxygen and then with aq NaOH, all three alkyl groups are converted into the corresponding alcohol in >90% yield. The course of the reaction may be depicted as shown in eq. 5.67.

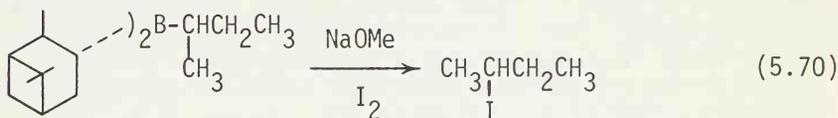
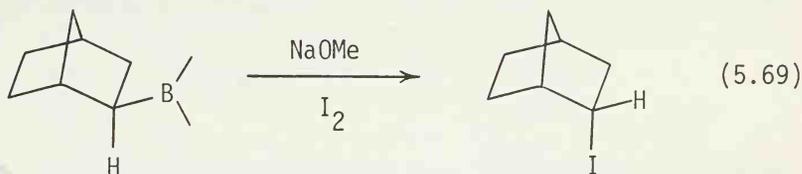


One drawback of the free-radical oxidation is that it is not stereospecific, for example, eq. 5.68.

Halogenolysis. Organoboranes themselves are relatively inert to iodine. Under basic conditions, however, a facile iodinolysis reaction takes place (5.58, 5.59). There is little doubt that the actual reactive species are organoborates. Indeed, lithium

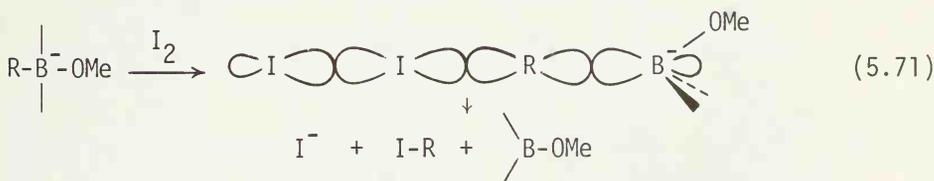


tetraalkylborates react with I_2 to give alkyl iodides (1 mole) and trialkylboranes (5.38). A recent study indicates that the reaction proceeds with inversion of configuration of the alkyl group; see eqs. 5.69, 5.70 (5.60).

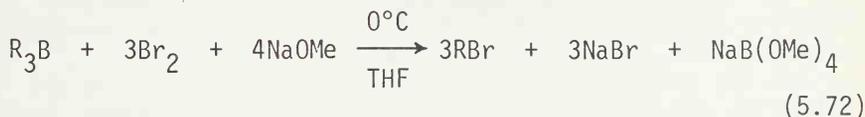


49% (84% optical purity)

The following S_H2 mechanism appears plausible.



A very similar reaction takes place between organoboranes and Br_2 ; see eq. 5.72 (5.61).



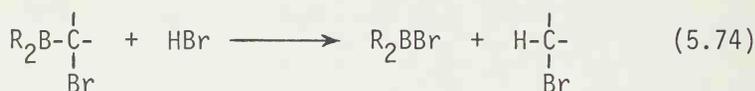
Primary alkyl bromides are usually obtained in excellent yields. Secondary alkyl bromides can also be prepared by this reaction,

although their yields are modest. This reaction also proceeds with inversion (5.62).

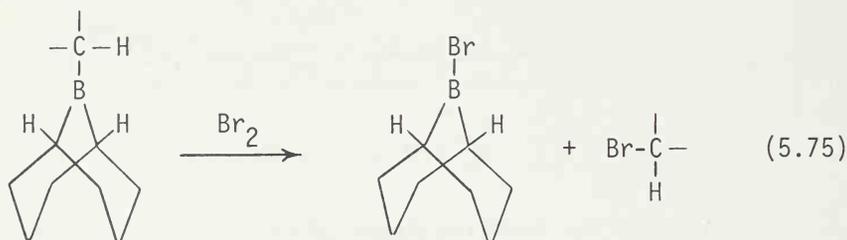
Under acidic or neutral conditions, an entirely different bromination reaction takes place, although the organic products are the same bromides, as shown in eq. 5.73.



A detailed study by Lane and Brown (5.63) has established that the reaction proceeds via the free-radical chain mechanism shown in eq. 5.54. The α -bromoalkylborane intermediate undergoes a slow protonolysis reaction with HBr formed under the reaction conditions (eq. 5.74). This protonolysis presumably is much faster than usual due to the presence of the α -bromine atom.



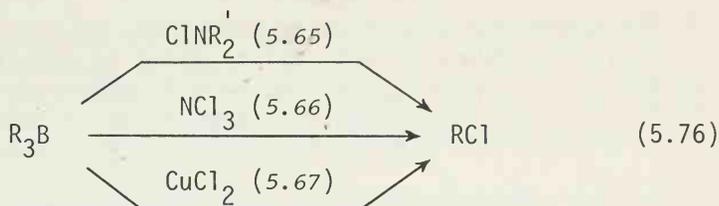
Secondary alkyl groups are considerably more reactive than primary alkyl groups in sharp contrast with the order of reactivity observed in the ionic bromination reaction. Tertiary alkyl groups which do not have any α -hydrogen should be inert. The use of B-alkyl-9-BBN permits a near complete conversion (80 to 90%) of olefins into alkyl bromides; see eq. 5.75 (5.64). The 9-BBN moiety does not competitively react, because its rigid conformation is such that an effective p_{π} - p_{π} delocalization between the α -free radical and the empty boron p orbital is prohibited.



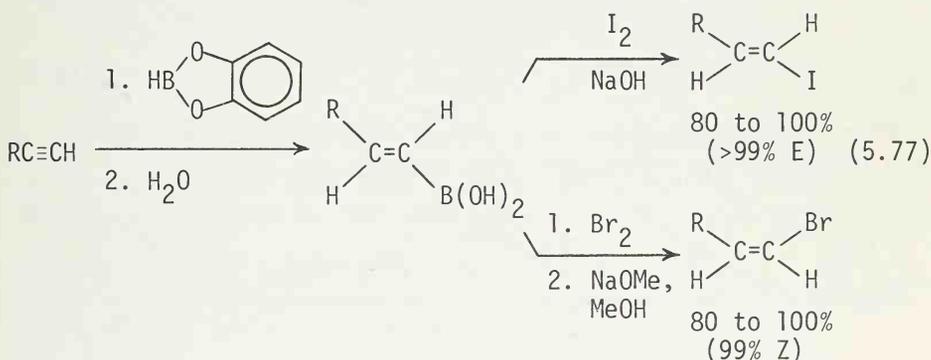
The α -bromoalkylboranes formed as intermediates undergo a fascinating carbon-carbon bond-forming reaction in the presence of a nucleophile, as discussed later.

A few reactions that convert organoboranes into alkyl chlorides are known (eq. 5.76). Their synthetic scope, however, is not very clear.

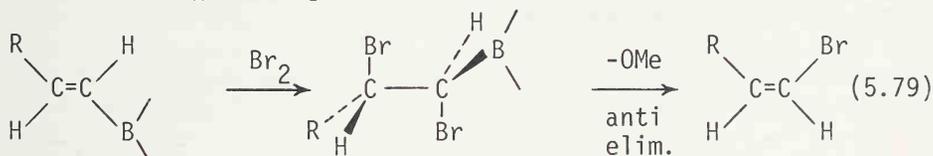
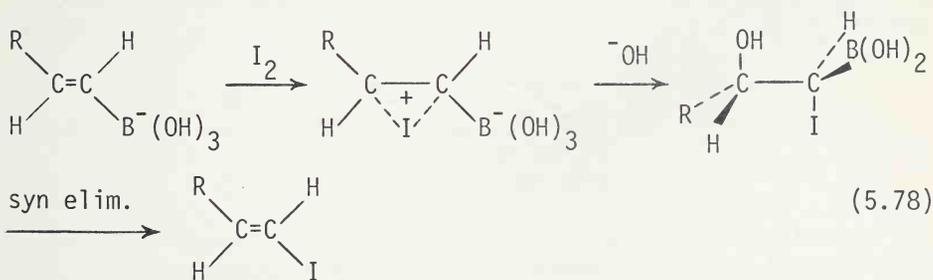
Alkenyl-, aryl-, and alkynylboranes can undergo entirely different reactions with halogens. Iodination and bromination



of alkenyl- and alkynylboranes can induce a highly unique carbon-carbon bond formation, as discussed later. When no carbon-carbon bond formation is possible, as in the reaction of alkeneboronic acids with I_2 or Br_2 , the corresponding organic halides can be prepared in high yields. The following syntheses of alkenyl iodides and bromides (5.68) are attractive and unique in that the required alkeneboronic acids can be obtained readily via hydroboration (eq. 5.77).

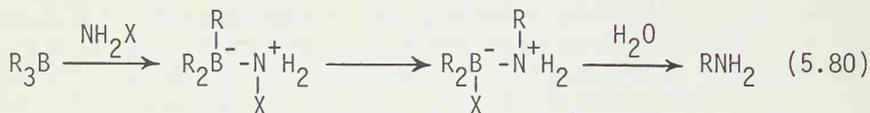


The diametrically opposed stereochemical results are intriguing, and have been interpreted as follows.

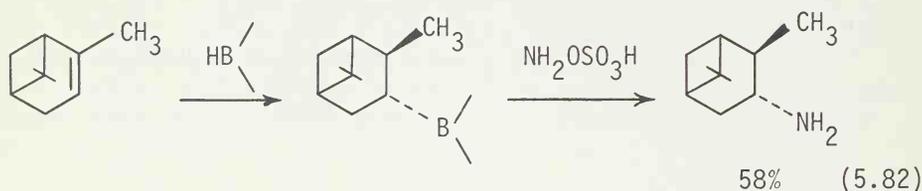


In the absence of a good nucleophile, the bromination of alkenylboranes can produce (*E*)-alkenyl bromides in moderate yields (5.69). Unfortunately, the reaction is generally not highly stereospecific. There does not appear any obvious advantage in preparing aryl and alkynyl halides via organoboranes.

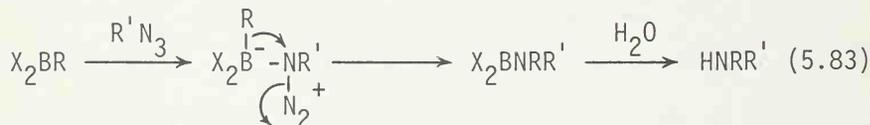
Amination. Amines containing good leaving groups such as NH_2Cl (5.70), $\text{NH}_2\text{OSO}_3\text{H}$ (5.71), 2,4,6- $\text{Me}_3\text{H}_2\text{C}_6\text{SO}_2\text{ONH}_2$ (5.72), and NMe_2Cl (5.65) can react with organoboranes (eqs. 5.80, 5.81).



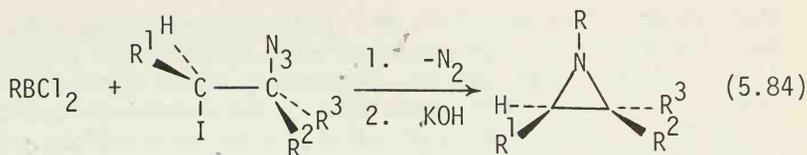
Olefins can be converted into stereo- and regiodefined amines via hydroboration-amination, for example, eq. 5.82.



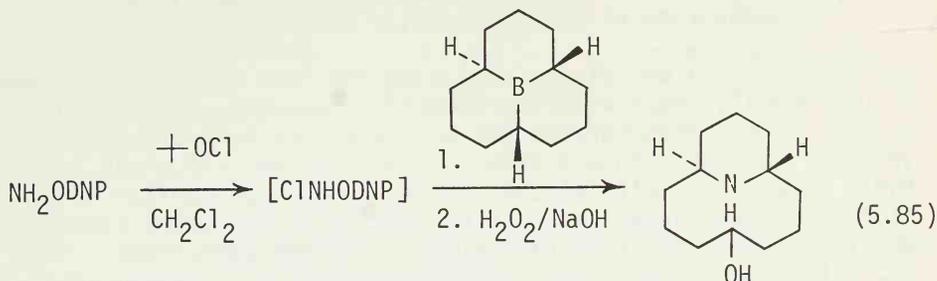
Alkyl and aryl azides react analogously with organoboranes; see eq. 5.83 (5.73).



The reaction of 2-iodoalkyl azides with organoboranes followed by treatment of the intermediates with KOH produces *n*-alkyl- and *n*-arylaziridines; see eq. 5.84 (5.74).



More recently, the following double alkyl migration reaction was introduced; see eq. 5.85 (5.75).



DNP = 2,4-dinitrophenyl

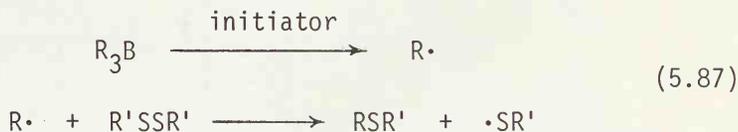
50%

It is important to note that all of these amination reactions can be rationalized by the same common 1,2-migration mechanism.

Formation of the Carbon-Sulfur Bond via Organoboranes. The reaction of trialkylboranes with alkyl and aryl disulfides produces dialkyl and alkyl aryl sulfides (5.76).



The reaction has been shown to proceed by a free-radical chain mechanism (q. 5.86).



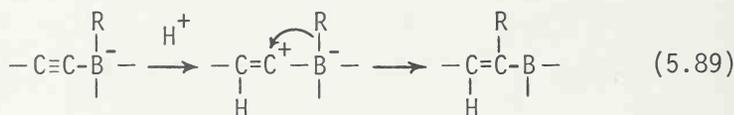
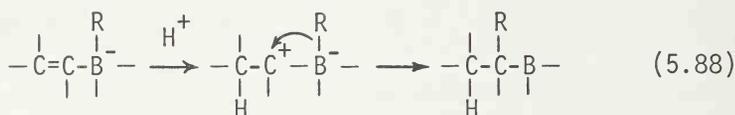
Transmetalation Reactions of Organoborons. Since boron is relatively electronegative, organoboron compounds do not readily serve as precursors of other organometallics. A significant exception is their reaction with mercuric salts to form organomercurials (Sect. 7.2.1). There have also been some indications

that other organometallics are formed as unstable intermediates. Thus treatment of organoboranes with Ag(I) salts produces the dimers of the alkyl groups, presumably via organosilver intermediates (5.77). More recently, it has been reported that the products of the reaction of alkenylboron derivatives with either Cu(I) salts or MeCu undergo reactions characteristic of organocoppers, as discussed in Sect. 9.1.

5.2.3.3 Formation of Carbon-Carbon Bonds via Reactions of Organoborons with Electrophilic Reagents

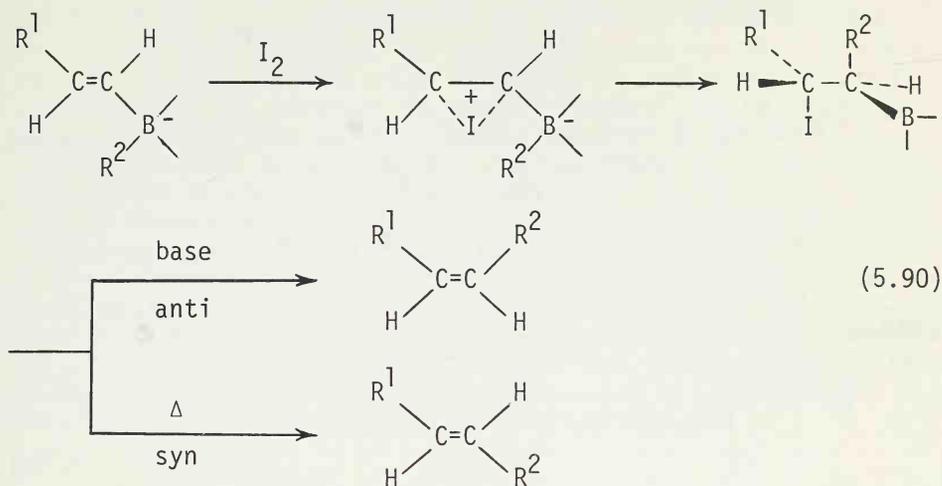
In Sect. 5.2.3.1 we briefly discussed the fact that organoboranes do not readily react with electrophilic reagents, whereas the corresponding organoborates can act as either Grignard-like reagents or undergo unique intramolecular transfer reactions in their interaction with electrophiles. Under appropriate conditions, however, organoboranes can react with so-called electrophilic reagents via free-radical or concerted mechanisms. Some typical carbon-carbon bond-forming reactions of organoboranes and organoborates with electrophilic reagents are discussed in this section.

Reaction with Proton Donors. Whereas alkyl-, aryl-, allyl-, and benzylboron derivatives undergo cleavage of the B-C bond with certain Brønsted acids, the corresponding reaction of alkenyl- and alkynylborates generally leads to the formation of a carbon-carbon bond between two boron-bound organic groups via 1,2-migration (eqs. 5.88, 5.89).

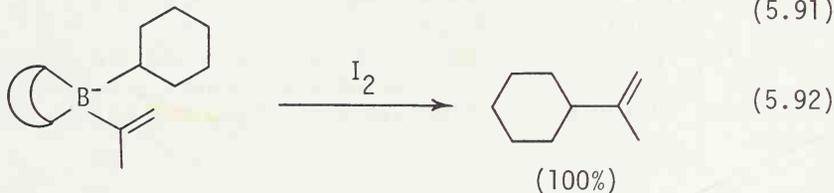
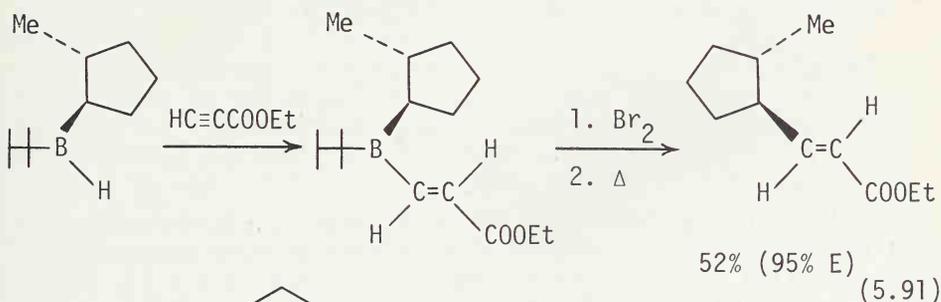


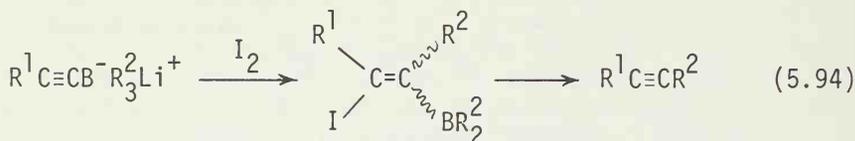
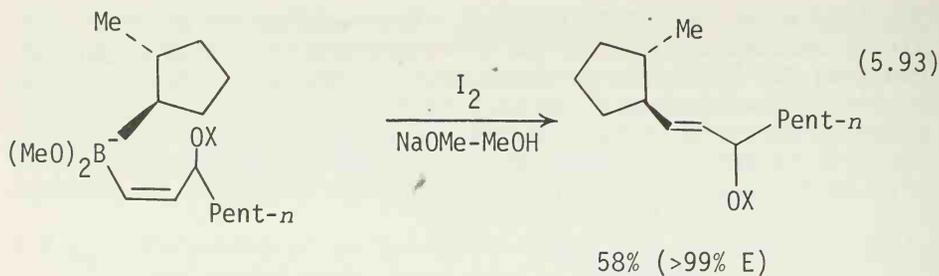
The reaction provides a route to certain Markovnikov organoboranes which cannot be readily prepared by hydroboration (5.78). The organoborane intermediates have been converted into alcohols, aldehydes, or ketones via oxidation (5.78, 5.79) or olefins via protonolysis (5.80) or dehydroboration (5.81).

Reaction with Iodine and Bromine. The reaction of alkenyl- and alkynylborates can provide an efficient and selective method of coupling two unlike boron-bound groups. Di- and trisubstituted olefins, shown in eqs. 5.90 to 5.93 (5.82 to 5.85), acetylenes, shown in eq. 5.94 (5.86 to 5.88), conjugated enynes, shown in eq. 5.95 (5.89), conjugated diynes, shown in eq. 5.96 (5.90), have been prepared in high yields.

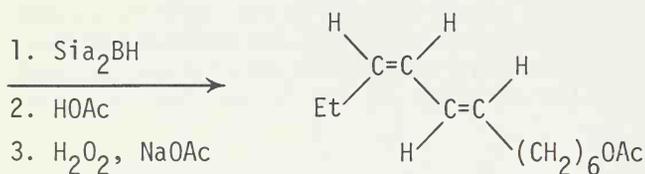
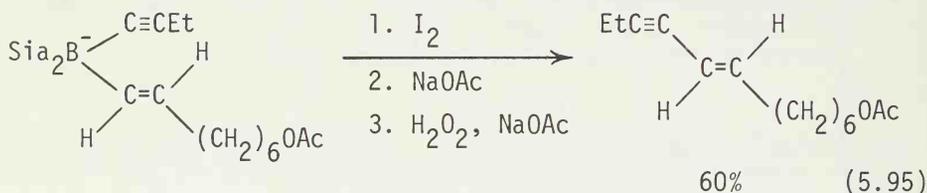


The use of *thexylborane* (5.83), *9-BBN* (5.84), or *alkaneboronic acids* (5.85) permits, in some favorable cases, a high-yield conversion of the alkyl or alkenyl group on the boron atom into the desired product.



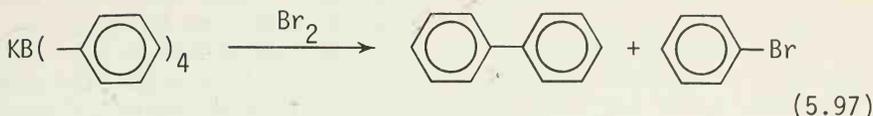


$R^1 = \text{H}$ or an organic group, $R^2 = 1^\circ, 2^\circ$, alkyl, or aryl



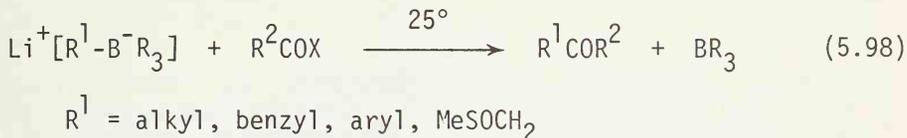
It should be noted that these intramolecular coupling reactions of organoborons provide viable alternatives to more conventional cross-coupling reactions involving Li, Mg (Sect. 4.3.2.1), Cu (Sect. 9.1), and Ni or Pd (Sect. 9.2).

A few related reactions of tetraarylborates are known; see eq. 5.97 (5.91). Currently available procedures, however, do not appear suitable for selectively coupling two unlike aryl groups.



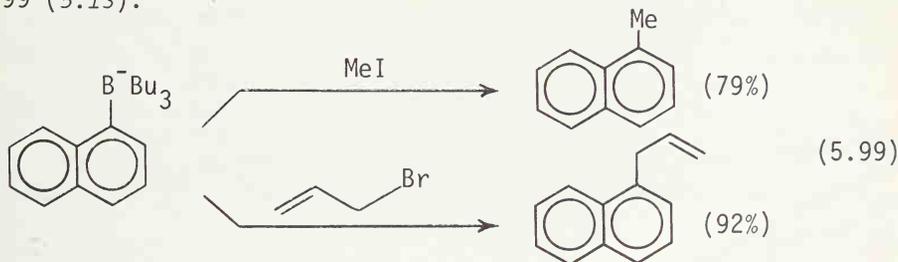
Reactions with Alkyl Halides, Acyl Halides, and Epoxides. As mentioned earlier, organoboranes are generally inert to alkyl halides and acyl halides. While organoboranes may act as catalysts for the polymerization of epoxides, no carbon-carbon bond between these two reagents is readily formed. The nucleophilicity of the B-C bond can be markedly enhanced by converting organoboranes into organoborates. The reactions of organoborates with carbon electrophiles have recently been reviewed (5.13, 5.36). Therefore only a very brief discussion is presented here.

(a) Intermolecular transfer reactions. The Grignard-like reaction, that is, intermolecular transfer reaction, of organoborates is relatively rare. Acyl halides represent about the only class of carbon electrophiles that can readily participate in the intermolecular transfer reaction; see eq. 5.98 (5.92). This ketone synthesis is highly chemoselective.



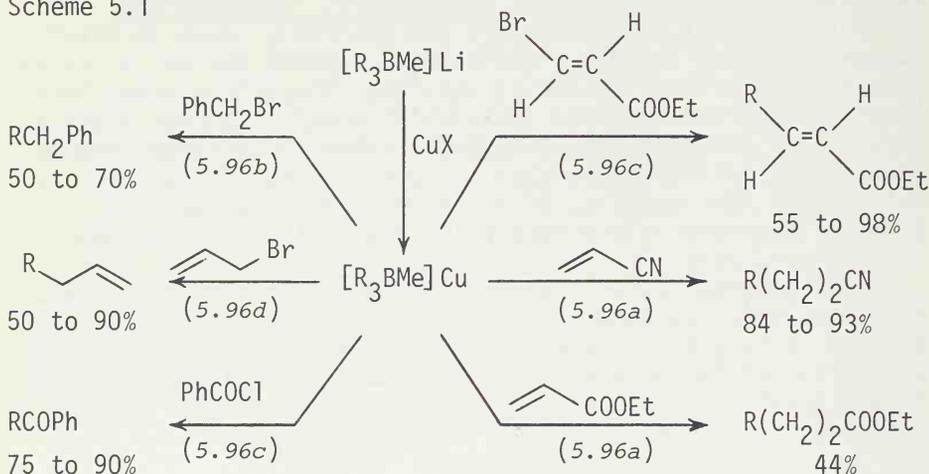
Even acyl halides preferentially undergo the intramolecular transfer reaction with cyanoborates (5.93), alkenyl- and alkynylborates (5.94), and thioalkoxymethylborates (5.95).

Alkyl halides and epoxides are generally quite reluctant to participate in the intermolecular transfer reaction. Only highly reactive alkyl halides, such as MeI and allyl bromides, react with lithium arylborates and sulfinyl- and sulfonyl-substituted lithium borates to form cross-coupled products, for example, eq. 5.99 (5.13).



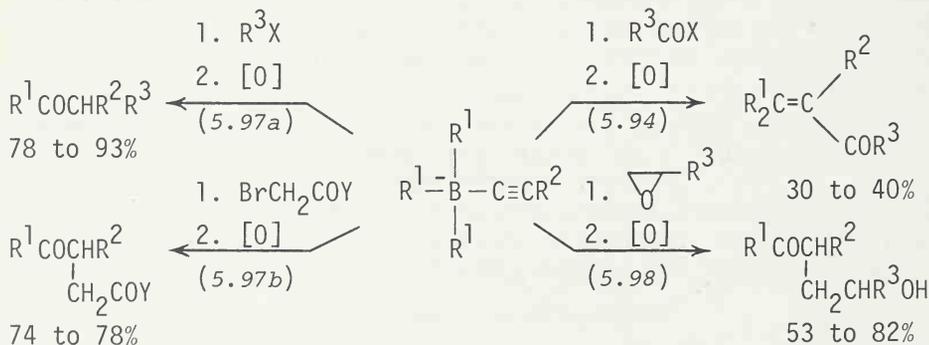
More recently, however, it has been found that the intermolecular transferrability of organoborates can be enhanced by forming copper(I) borates, as indicated in Scheme 5.1 (5.96). Despite these promising new developments, it may be said that the intermolecular transferrability of organoborates is generally low and that organoboranes are quite nonnucleophilic.

Scheme 5.1

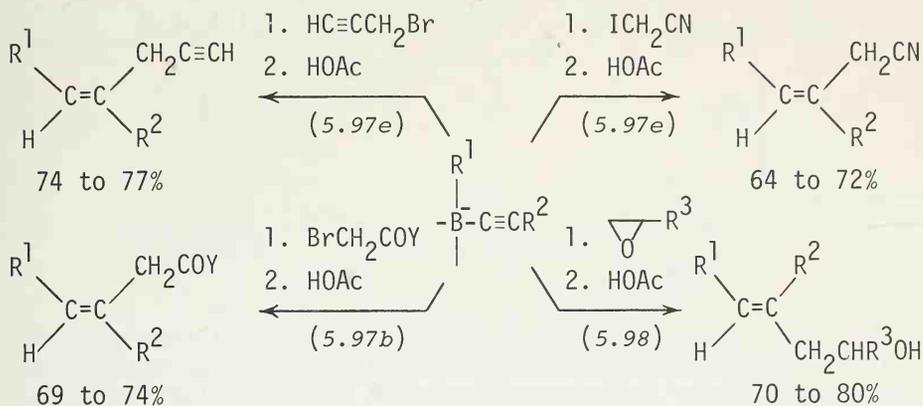


(b) Intramolecular Transfer Reactions. α,β -Unsaturated organoborates, in particular alkynyl-, alkenyl-, and cyanoborates, have a strong tendency to undergo the intramolecular transfer reaction (eqs. 5.42 to 5.44). The organoborane products thus formed can be either oxidized or subjected to protonolysis to obtain organic products. Some typical results are summarized in Schemes 5.2 to 5.4.

Scheme 5.2

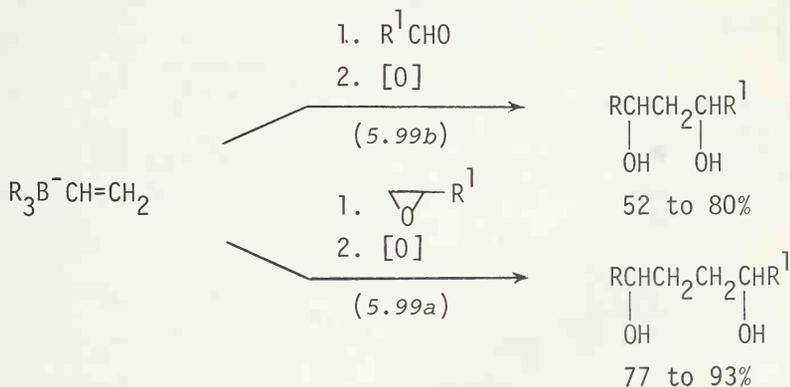


Scheme 5.3



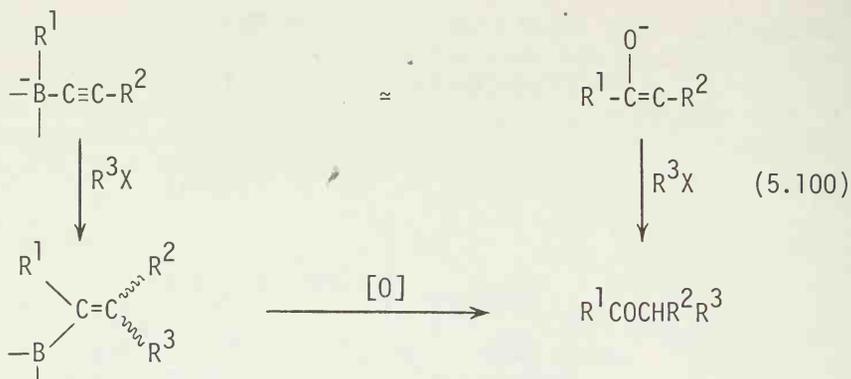
Unlike the reaction with simple alkyl halides, such as MeI, the reactions shown in Scheme 5.3 are reasonably stereoselective (>90%). The stereochemistry of these reactions, however, is somewhat unpredictable and difficult to rationalize.

Scheme 5.4

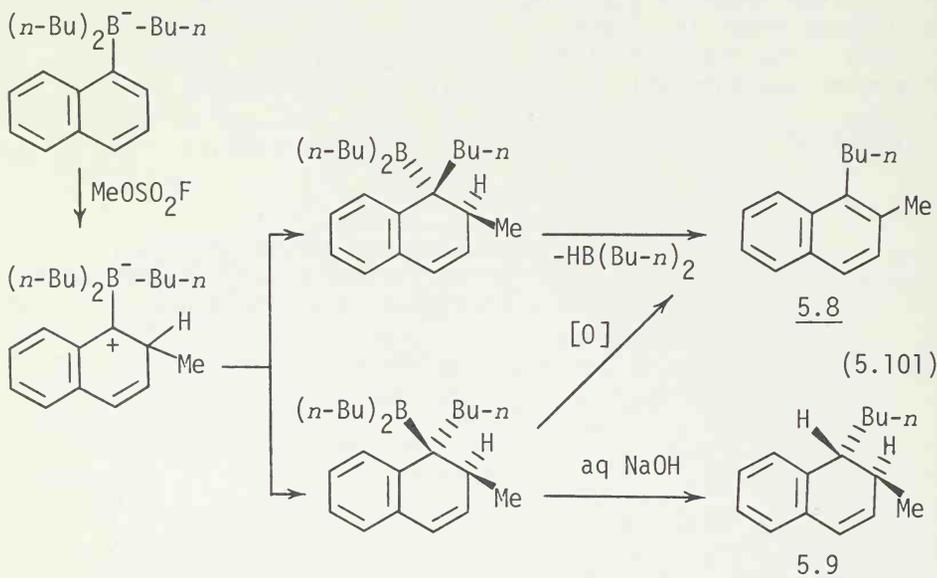


It is useful to note that alkynylborates can act as enolate equivalents in some of these reactions, for example, eq. 5.100.

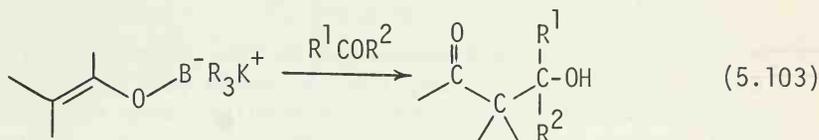
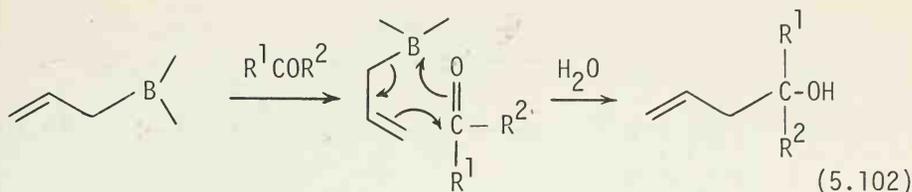
The alkylation of arylborates can proceed either via intermolecular transfer, for example, eq. 5.99, or via intramolecular transfer (5.100). For example, the reaction of $LiB_u_3^-(Naph)$ with CH_3OSO_2F produces the double alkylation product 5.8 in 70% yield after oxidation and the dihydroaromatic derivative



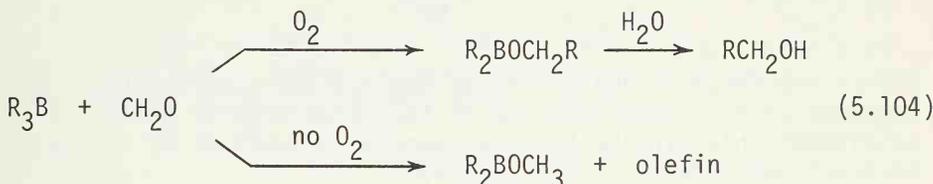
5.9 in 56% yield along with a 22% yield of 5.8 after hydrolysis. The results can be interpreted in terms of intramolecular 1,2-migration (eq. 5.101).



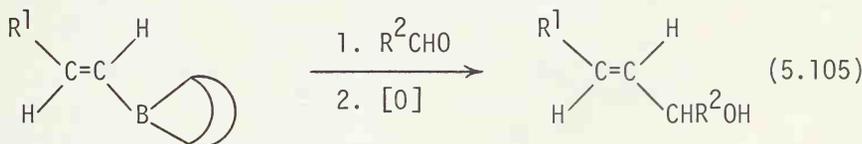
Reactions with Aldehydes, Ketones, and α,β -Unsaturated Carbonyl Compounds. Ordinary ketones are generally quite inert to organo-borons, although allylboranes, shown in eq. 5.102 (5.101), enolboranes, shown in eq. 5.50 (5.102), and enolborates, shown in eq. 5.103 (5.103), react with ketones.



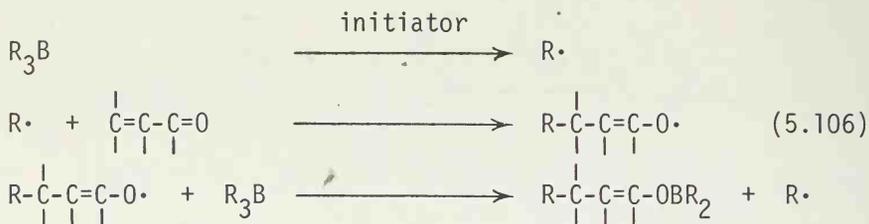
The reactions of allylboranes and enolboranes appear best viewed as $[2_s + 4_s]$ pericyclic processes. Aldehydes have participated in other reactions with organoborons as well. Their reaction with alkenylborates is shown in Scheme 5.4. Monomeric formaldehyde reacts with organoboranes to give one-carbon homologated alcohols in the presence of air; see eq. 5.104 (5.104).



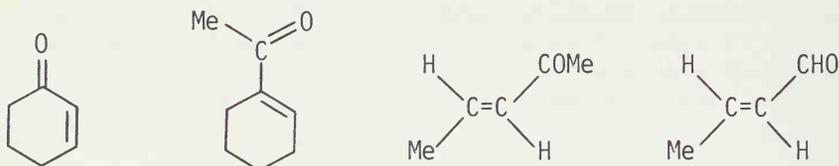
More recently, it has been shown that alkenyl-9-BBNs undergo a Grignard-like addition reaction with aldehydes at 65°C . The yields of the products, however, are generally modest (5.105).



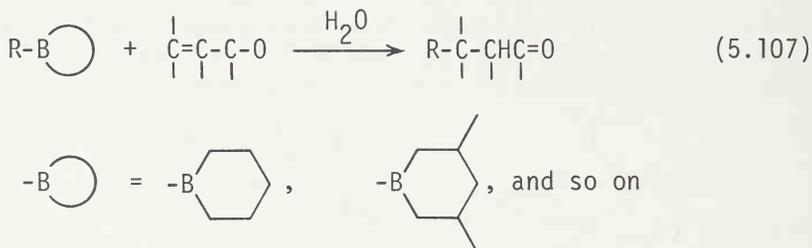
Unlike simple aldehydes and ketones, their α,β -unsaturated derivatives are quite reactive toward organoboranes. Most of the earlier results have been thoroughly reviewed (5.3 to 5.6, 5.106). Many, but not all, of these reactions have been shown to proceed by a free-radical chain mechanism (eq. 5.106). The reactions of β -unsubstituted enones are very facile and uniquely useful in that most of the other conjugate addition reactions, such as those involving copper (Sect. 9.4), tend to give poor results with these unhindered enones. Methyl vinyl ketone, acro-



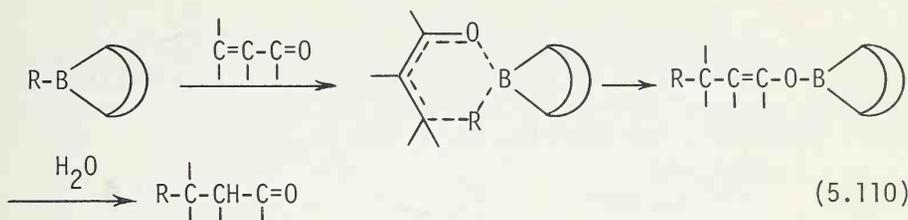
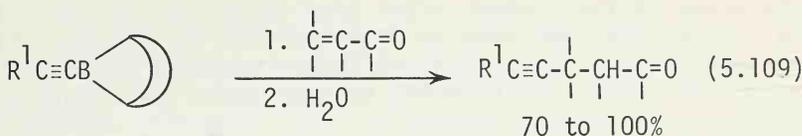
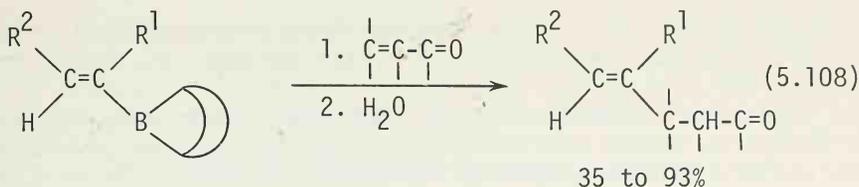
lein, α -methyl-, and α -bromoacroleins have reacted satisfactorily (5.107). On the other hand, the conjugate addition reaction of β -monosubstituted enones generally requires some external free-radical source, such as O_2 , peroxides, and light. Under these conditions, the following enones have reacted with organoboranes to give 1,4-adducts (5.108).



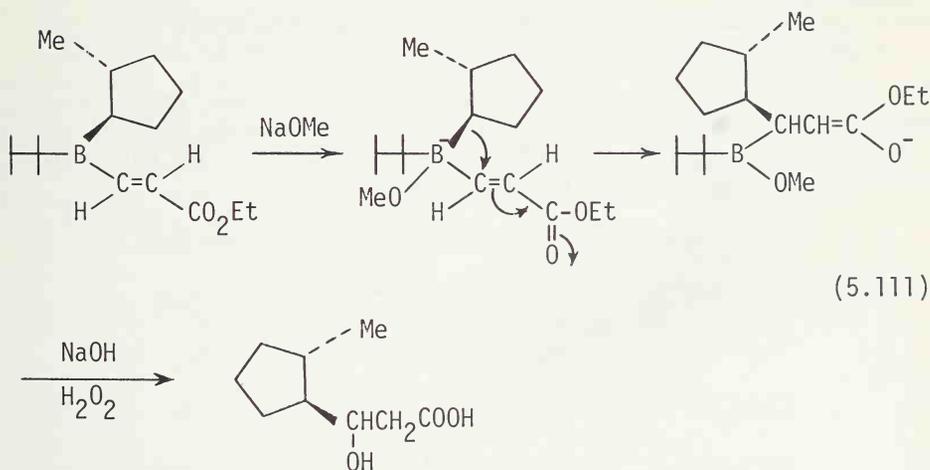
One of the serious limitations of the 1,4-addition reactions of organoboranes is that only one of the three organic groups is utilized. This problem has been partially overcome by β -alkylboracyclanes; see eq. 5.107 (5.109).



It has recently been reported that alkenyl- and alkynyl-9-BBNs react with enones to produce 1,4-adducts (5.110). Even some β,β -disubstituted enones have reacted, albeit slowly. Enones capable of assuming a cisoid conformation react, whereas transoid enones have not. These results are not consistent with the free-radical mechanism presented above. The following six-centered pericyclic mechanism has been suggested as a plausible path (eq. 5.110).



Organoborates should be capable of undergoing conjugate addition reactions. Indeed, a very facile conjugate addition takes place intramolecularly; see eq. 5.111 (5.111).

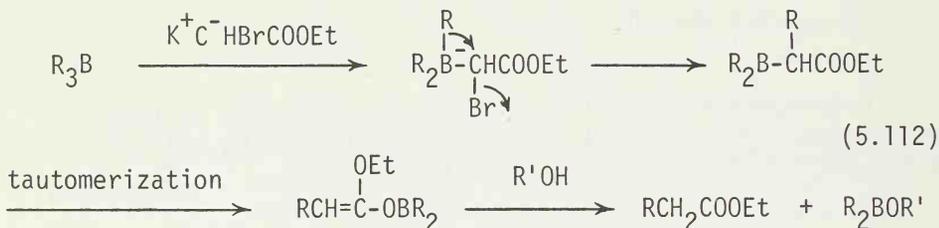


More recently, a few intermolecular conjugate addition reactions of organoborates involving CuBR_4 (5.96a) and alkynylborates (5.112) have been reported. The full scope of such reactions, however, remains to be further explored.

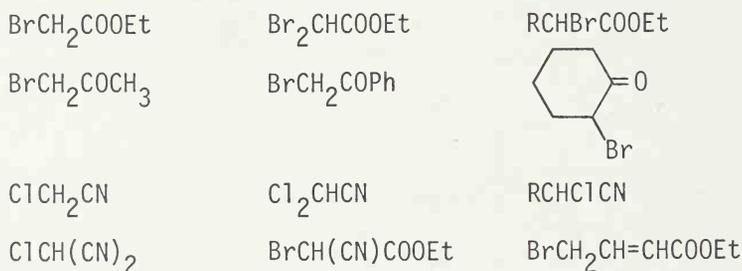
5.2.3.4 Formation of Carbon-Carbon Bonds via Reactions of Organoboranes with Nucleophilic Reagents

In Sect. 5.2.3.1 we discuss the fact that organoboranes react with appropriately substituted nucleophiles to undergo the intramolecular transfer reactions represented by eqs. 5.34 to 5.36. The scope of the carbon-carbon bond formation via the intramolecular transfer reactions of organoboranes is so broad that it is not possible to discuss all of these reactions in detail in this book. The reader is referred to monographs cited earlier (5.3 to 5.6) and a general review (5.113). Specific reviews are cited later.

Reactions with α -Hetero-Substituted α -Carbonyl Carbon Nucleophiles. The reaction of organoboranes with α -halo enolate anions provides a useful method for α -alkylation and α -arylation of carbonyl compounds, for example, eq. 5.112 (5.114).



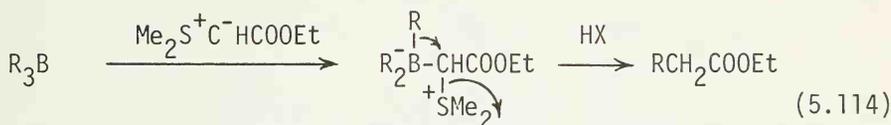
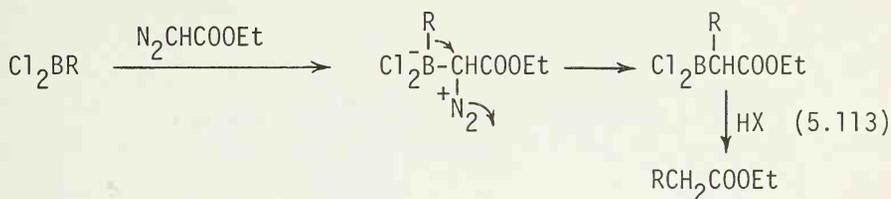
The unusually facile protonolysis involves the reaction of enolboranes formed via tautomerization (5.115). A wide variety of α -halo enolate anions, such as those derived from the following compounds, undergo this alkylation reaction.



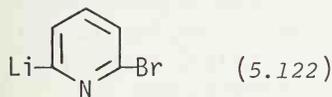
The following observations are worth noting: (1) Introduction of hindered and/or stereo-defined alkyl groups and aryl groups in the α -position of carbonyl compounds can now be achieved. (2)

α,α -Dihalo enolate anions can be converted into either α -halo- α -alkyl or α,α -dialkyl derivatives. (3) The use of B-alkyl-9-BBNs permits a high-yield conversion of the alkyl group into two-carbon homologated carbonyl compounds (5.116). (4) In some cases, the use of highly hindered phenolate bases, for example, potassium 2,6-di-*t*-butylphenolate, is either necessary or advantageous (5.117).

Related to these alkylation reactions are the reactions of organoboranes with α -diazo carbonyl compounds, for example, eq. 5.113 (5.118), and the corresponding sulfur ylides, for example, eq. 5.114 (5.119).

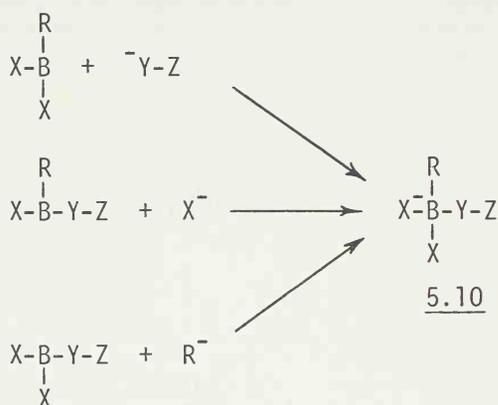


If the mechanism proposed for these reactions were correct, the presence of an α -carbonyl group is not a necessary requirement. Various other α -hetero-substituted carbon nucleophiles should also undergo similar intramolecular transfer reactions. Indeed, a number of such carbon nucleophiles, such as those shown below, have been shown to undergo the expected intramolecular transfer reactions.



Reactions of α -Hetero-Substituted Organoboranes with Nucleophiles. Inspection of the structure of the presumed key intermediate (5.10) in the intramolecular transfer reaction of organoboranes discussed above suggests that, in addition to that route, there are at least two other conceptually and practically different routes to 5.10 as shown in Scheme 5.5.

Scheme 5.5

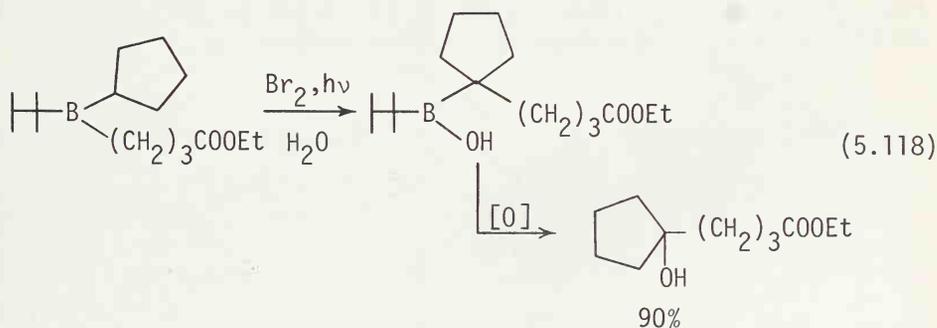
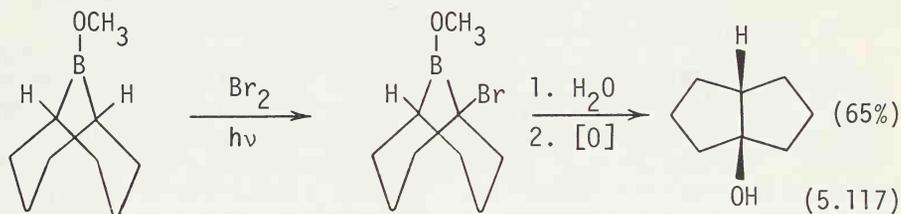
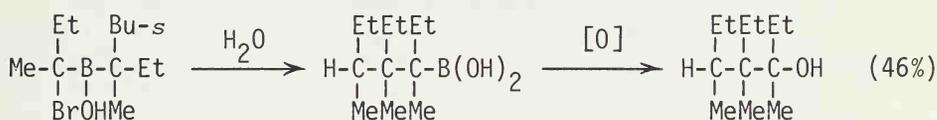
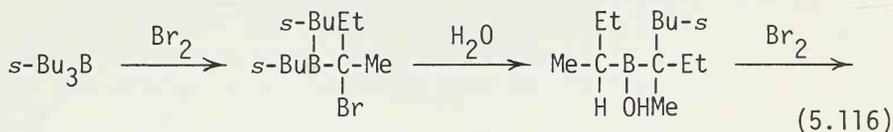
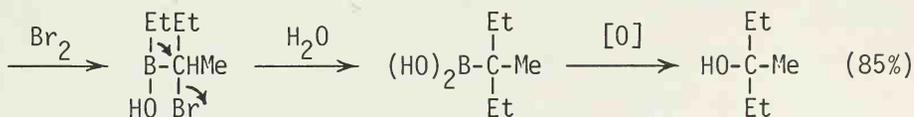
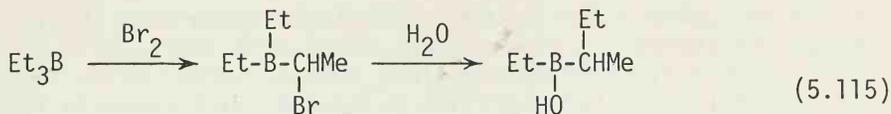


If the hypothetical species 5.10 were indeed intermediates of these reactions, the same products should be obtained regardless of the method of their generation. There can be, however, major differences in product yield, ease of generation of 5.10, and other significant aspects of the reaction.

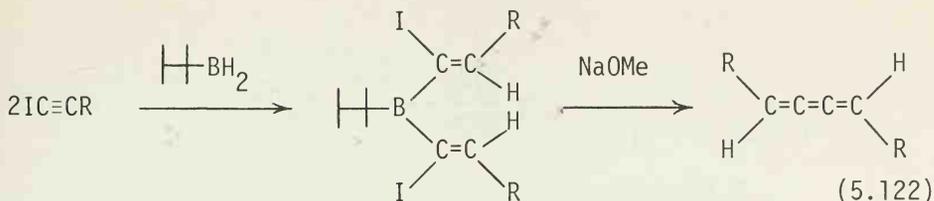
The required appropriately α -hetero-substituted organoboranes can be prepared by various methods, of which the free-radical bromination of organoboranes (Sect. 5.2.3.2) and the hydroboration of haloalkenes and haloalkynes (Sect. 5.2.2.2) have been most widely used. A brief discussion of the reactions of such organoboranes is presented below.

(a) Reaction of α -bromoboranes obtained via bromination of organoboranes. The reactions of triethylborane and tri-*sec*-butylborane with Br_2 in the presence of H_2O have been shown to proceed by the following mechanisms, in which the free-radical bromination and the intramolecular 1,2-migration alternate; see eqs. 5.115, 5.116 (5.127).

These reaction sequences provide a unique method for coupling two boron-bound alkyl groups, as exemplified by eq. 5.117 and 5.118 (5.128, 5.129).



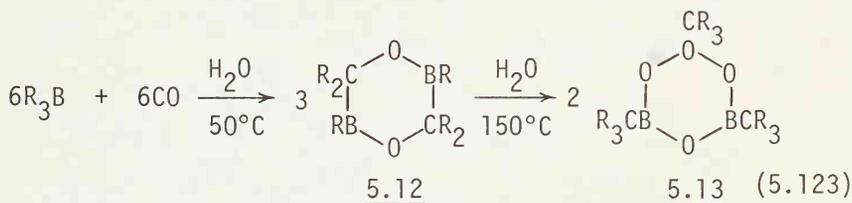
(b) Reaction of α -haloboranes obtained via hydroboration. As discussed in Sect. 5.2.2.2, hydroboration of alkenyl and alkynyl halides produces α -haloboranes. Especially noteworthy is the



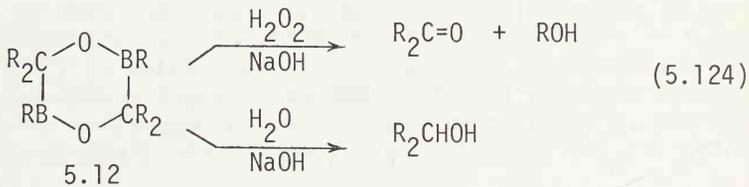
Carbonylation and Related Reactions of Organoboranes. (a) Carbonylation. All of the 1,2-migration reactions of organoboranes discussed so far are represented by either eq. 5.34 or eq. 5.35. Let us now discuss some reactions that can be represented by eq. 5.36.

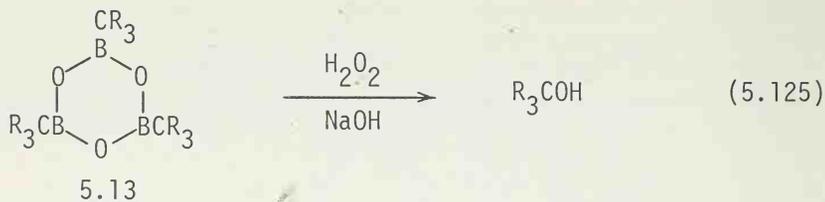
The reaction of organoboranes with CO is one of the most general and versatile reactions which organoboranes undergo. A variety of primary, secondary, and tertiary alcohols, aldehydes, and ketones have been synthesized by this reaction. Since this reaction has been extensively reviewed (5.3 to 5.6, 5.134, 5.135), only a brief summary is presented here.

In 1962 Hillmann (5.136) reported that trialkylboranes reacted with CO at about 10,000 psi at 25 to 75°C to form 2,5-dibora-1,4-dioxanes (5.12). At >140°C, 5.12 were smoothly converted into the corresponding boroxines 5.13. In the absence of protic solvents, mixtures of 5.12 and 5.13 are formed. No interconversion between 5.12 and 5.13 takes place even at 200°C.



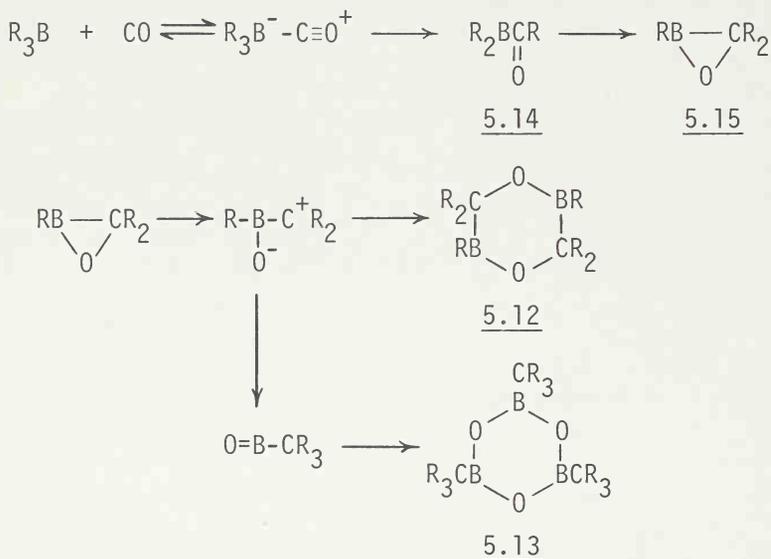
Oxidation of 5.12 produces a 1:1 mixture of a ketone ($\text{R}_2\text{C}=\text{O}$) and an alcohol (ROH), whereas its hydrolysis gives a dialkylcarbinol (R_2CHOH). On the other hand, oxidation of 5.13 gives the corresponding trialkylcarbinol (R_3COH).



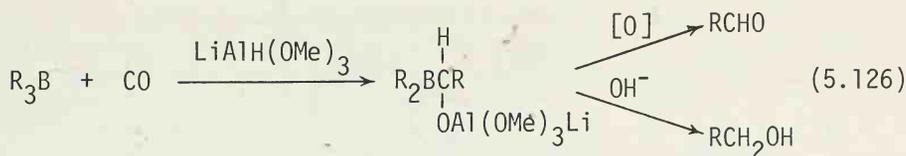


Subsequent studies by Brown (5.137) have established that, in many cases, the reaction proceeds even at atmospheric pressure. Since the reaction of two different organoboranes does not give any crossover product, the transfer of the alkyl groups from boron to carbon must be an intramolecular process. The following mechanism is consistent with the available data (Scheme 5.6).

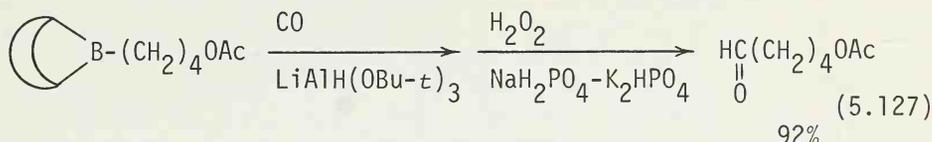
Scheme 5.6



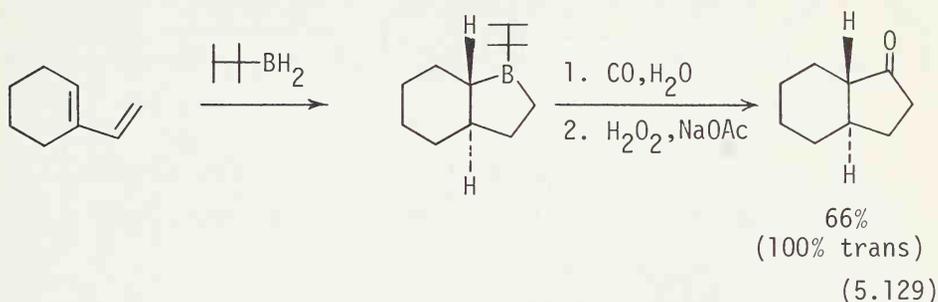
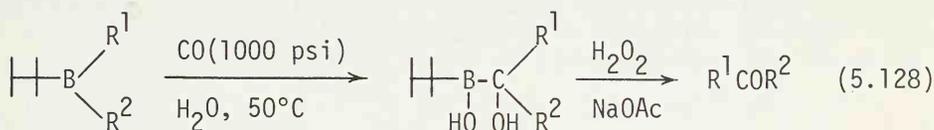
Under the usual carbonylation conditions, it has not been possible to obtain the product of single alkyl migration 5.14. It has, however, been possible to stop the reaction after migration of one alkyl group by carrying out the reaction in the presence of $\text{LiAlH}(\text{OMe})_3$. On oxidation of the intermediates thus obtained, aldehydes were formed in high yields (5.138). It has also been possible to obtain the corresponding methylols (5.139). The use of 9-BBN permits a high-yield conversion of olefins into aldehydes, while $\text{LiAlH}(\text{OBu}-t)_3$ makes this aldehyde synthesis



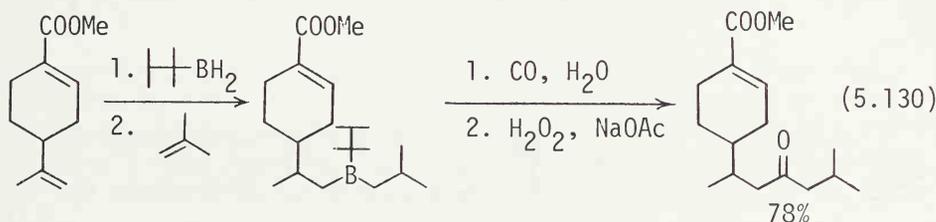
highly chemoselective, for example, eq. 5.127 (5.140).

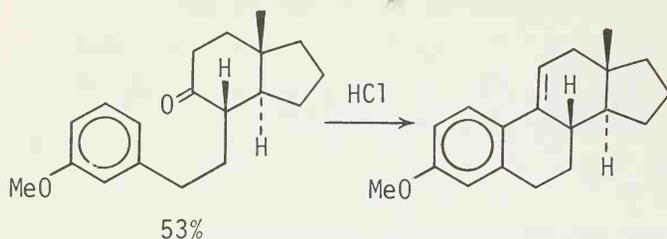
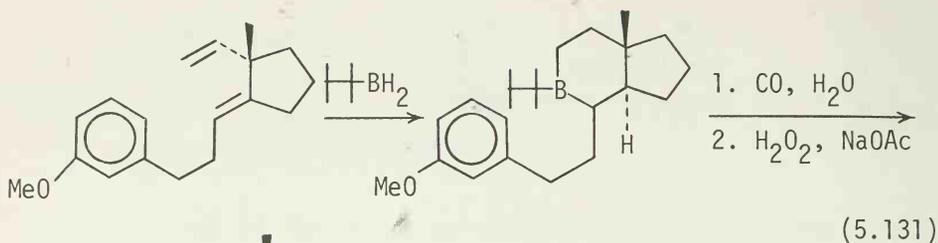


The thexyl group exhibits a very low migratory aptitude for migration in the carbonylation of thexyl dialkylboranes. This makes it possible to synthesize mixed and cyclic ketones in high yields; see eqs. 5.128, 5.129 (5.141).

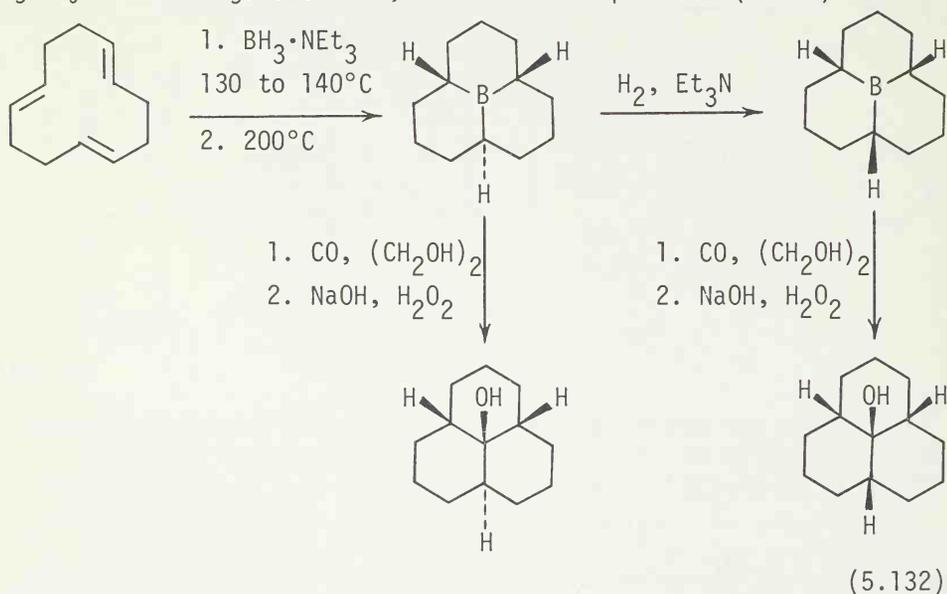


This ketone synthesis has been applied to the syntheses of juvabione, shown in eq. 5.130 (5.142), and a steroidal compound, shown in eq. 5.131 (5.143).





The carbonylation of organoboranes at 150°C in the presence of a protic solvent followed by oxidation provides a means for converting organoboranes into the corresponding carbon structures with complete retention of the overall and stereochemical integrity of the organoboranes, as shown in eq. 5.132 (5.144).

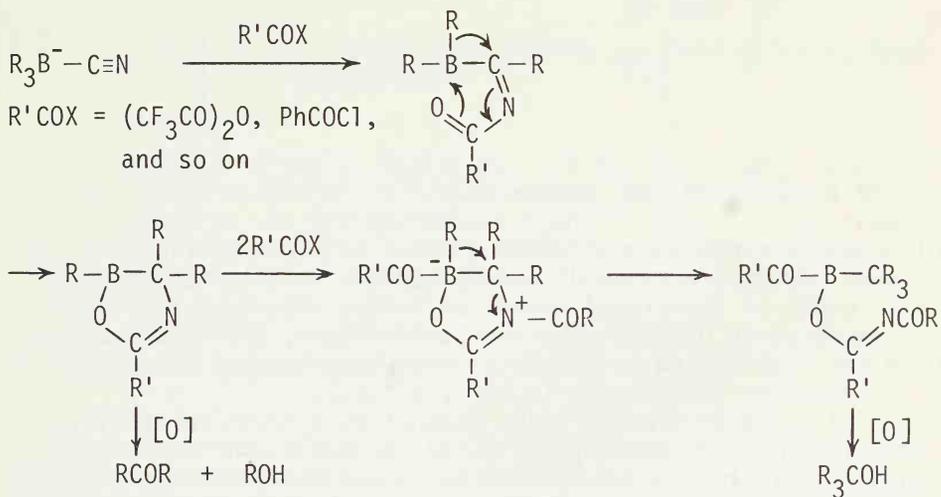


Although CO does not require a more complicated apparatus than that which catalytic hydrogenation requires, and is therefore not inconvenient to use, there exists an unfortunate but

prevailing tendency among practicing chemists to avoid CO in laboratories. More recently, a few organoboron reactions, which allow transformations similar to those discussed above, have been developed.

(b) The reaction of cyanoborates with electrophiles. Treatment of trialkylboranes with KCN or NaCN produces the corresponding trialkylcyanoborates, which are isoelectronic with the trialkylborane-CO adducts in Scheme 5.6. Trialkylcyanoborates, however, do not undergo spontaneous 1,2-migration, presumably due to the lack of an electrophilic migration terminus. The earlier discovery by Köster (5.145) that the 1,2-migration of alkynylborates can be induced by their treatment with electrophiles led Pelter (5.93, 5.146) to develop a closely related cyanoborate-electrophile reaction. Trifluoroacetic anhydride (TFAA) has been used most extensively as the required electrophile. The reaction is applicable to the synthesis of ketones and dialkyl- and trialkylcarbinols. Aldehydes have not yet been prepared by this reaction. The results obtained to date may be represented by the following scheme.

Scheme 5.7

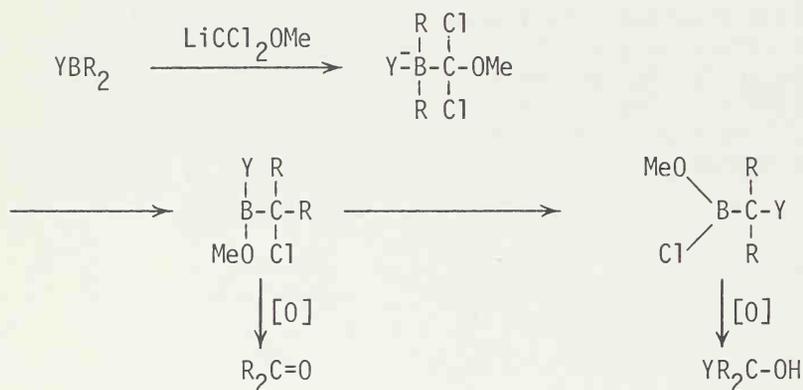


It appears that virtually all of the compounds that have been prepared by this reaction can also be prepared by the carbonylation reaction. On the other hand, it is not clear to the author if the reverse is also true. It should be noted that the cyanoborate-electrophile reaction requires a strong Lewis acid, such

as TFAA. Thus those functional groups that are destroyed by such reagents may not be tolerated.

(c) The reaction of organoboranes with polyhalocarbanions. One serious limitation associated with both the carbonylation and the cyanoborate-electrophile reaction is that only triorganoboranes can be used successfully. It is often advantageous to be able to use dialkylborane derivatives in the synthesis of ketones and dialkylcarbinols. This problem has been partially overcome by the development of the reaction of organoboranes with lithiodichloromethyl methyl ether as shown in Scheme 5.8 (5.147).

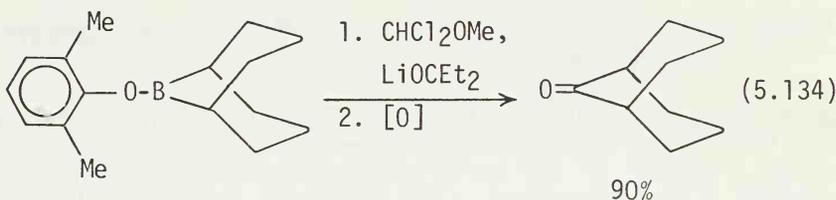
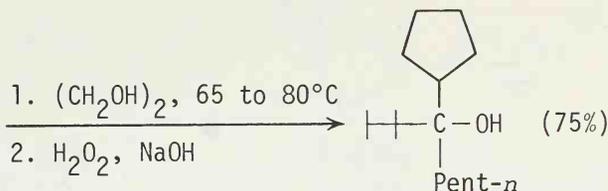
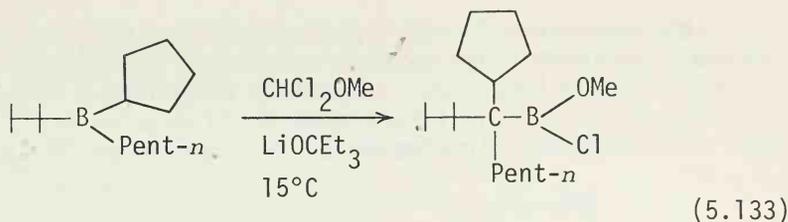
Scheme 5.8



Y = alkyl, OH, OR, and so on

Although this reaction is nothing but a triple-migration version of some of the reactions discussed earlier in this section, the exact order of the ligand migration is not clearly established. In the reaction of dialkylboronic acid esters, the intermediates have been identified as either α -chloroboronic acid esters or α -methoxyboronic acid esters (5.147c, 5.147e).

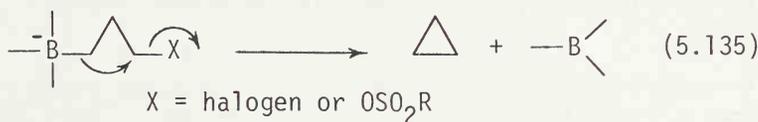
The reaction appears quite general as a route to trialkylcarbinols, as indicated by eq. 5.133 (5.147d). The following synthesis of bicyclo[3.3.1]nonan-9-one demonstrates a unique advantage of the reaction over the carbonylation or the cyanoborate-electrophile reaction; see eq. 5.134 (5.148). At present, the synthesis of ketones by this reaction requires dialkylborane derivatives. Thus the scope of the ketone synthesis is limited by the lack of a general route to mixed dialkylborane derivatives.



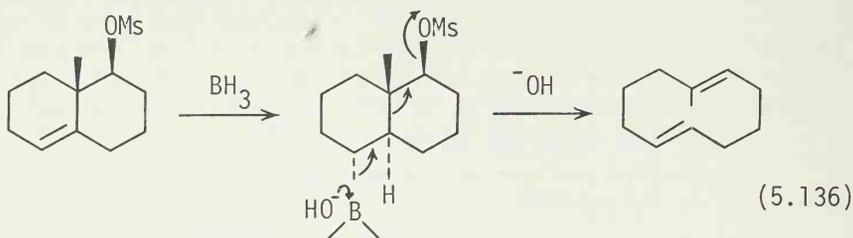
5.2.3.5 Other Carbon-Carbon Bond-Forming and Bond-Cleaving Reactions of Organoborons

Miscellaneous Elimination Reactions. It has been amply demonstrated that organoborons carrying a good leaving group in the α -position undergo the intramolecular transfer via 1,2-migration (eq. 5.34). We have also learned that those carrying a good leaving group in the β -position undergo β -elimination (eq. 5.90). Usually, the base-catalyzed elimination is an anti process, whereas the thermal elimination is a syn process. What about organoborons carrying a good leaving group in a more remote position?

(a) Cyclopropane synthesis via γ -elimination. Organoborons carrying a good leaving group in the γ -position undergo a facile γ -elimination to form cyclopropane derivatives; see eq. 5.135 (5.149).

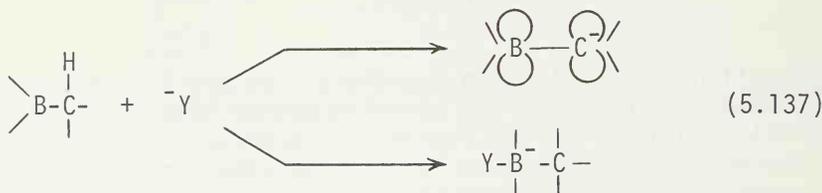


(b) Fragmentation reactions of δ -hetero-substituted organoborons. δ -Hetero-substituted organoborons can undergo either formation of cyclobutanes (5.149d) or a Grob-type fragmentation reaction (5.150). The latter appears to require rigid and favorable conformational arrangements, as shown in eq. 5.136.

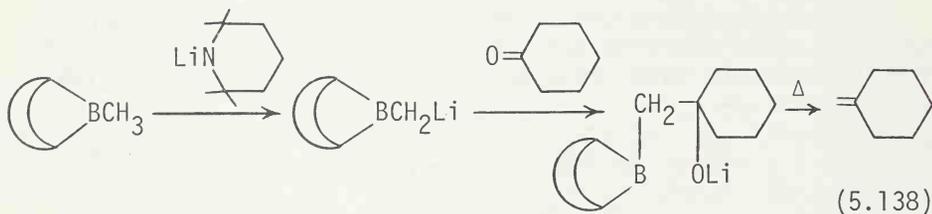


Little is known about the reaction of organoborons carrying more remote leaving groups.

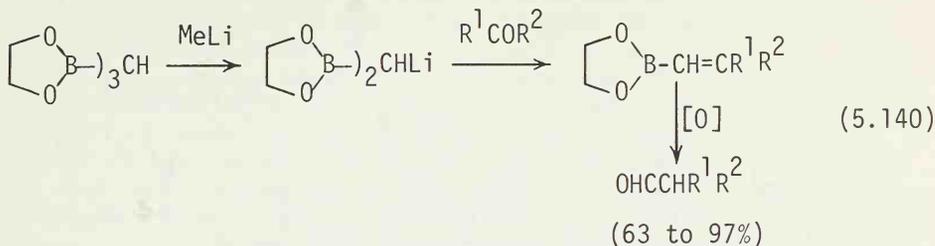
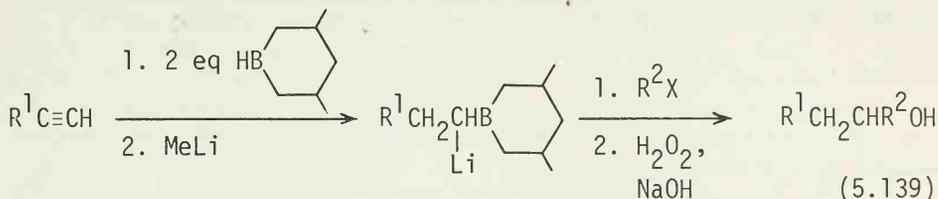
Generation and Reactions of Boron-Stabilized Carbanions. Just as the carbonyl group stabilizes an adjacent carbanionic center, the empty p orbital of the boron atom of organoboranes should also exhibit a similar effect. The intrinsic difficulty is how to generate such species without forming undesirable organoborate complexes.



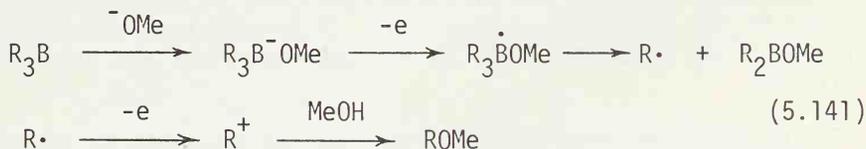
One successful approach involves the use of so-called highly basic but nonnucleophilic bases (5.151). The boron-stabilized carbanions thus generated can react with carbonyl compounds to undergo a Wittig-like reaction (eq. 5.138).



An alternate approach involves generation of *gem*-dibora and *gem*-tribora compounds followed by treatment with a base, for example, eqs. 5.139 and 5.140 (5.152, 5.153).



Miscellaneous One-Electron Transfer Reactions. It has been amply demonstrated that organoborons are good sources of carbon free-radicals. It now appears that, under electrolytic conditions, even carbocations can be generated from organoboranes via free radicals. The anodic oxidation of organoboranes using graphite as the anode produces alkyl methyl ethers, when carried out in the presence of NaClO_4 , NaOMe , and MeOH , and alkyl acetates, when carried out in the presence of NaOAc and HOAc (5.154). The formation of alkyl methyl ethers, for example, has been rationalized as follows.

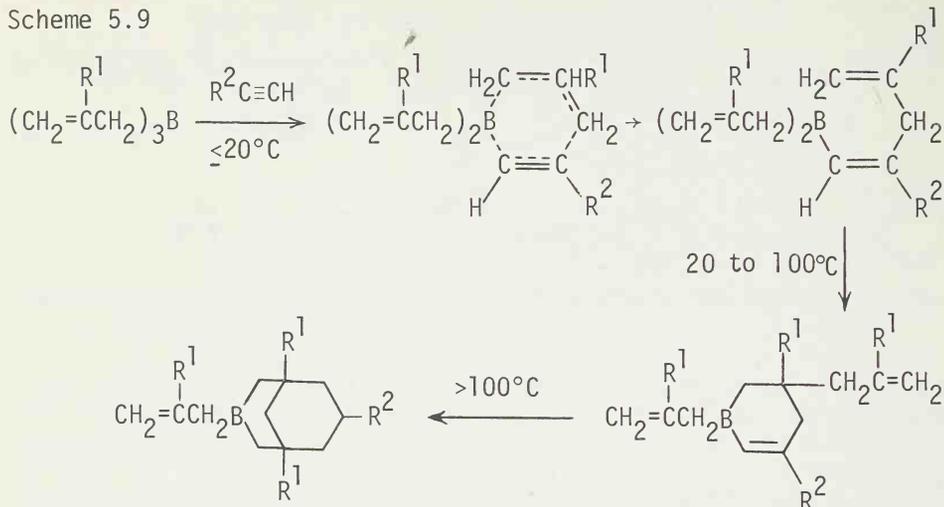


Electrolysis of organoboranes in CH_3CN (5.155a) and CH_3NO_2 (5.155b) has produced homologated nitriles and nitro compounds, respectively.

Carboboration Reactions. Unlike organoalanes, ordinary organoboranes do not readily undergo carbometallation with olefins and

acetylenes. Allylboranes, however, are exceptional and react with acetylenes and olefins to form the corresponding addition products (5.101), as shown in Scheme 5.9. The results have been interpreted in terms of a $[2_s + 4_s]$ process which is analogous to the "ene" reaction.

Scheme 5.9



The formation of the monocyclic intermediate involves an allylboration reaction of the terminal olefin group, whereas that of the bicyclic product must be a rare example of the addition of an alkenyl-boron bond to an olefin.

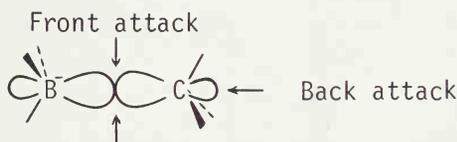
Miscellaneous Reactions. There can be a variety of organoborane reactions in which the boron atom acts as a carbonyl-like electron-withdrawing group. For example, there have been indications (5.156) that alkenyl- and alkynylboranes act as efficient dienophiles in the Diels-Alder reaction. Although highly promising, the scope and synthetic utility of such reactions are yet to be explored.

5.2.3.6 Organoboranes and Organoborates as Reagents in Organic Synthesis

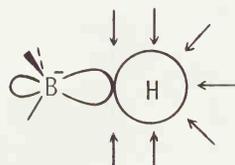
The single most important application of organoboranes and organoborates to organic synthesis is the reduction of organic compounds with these reagents via hydride transfer. Some representative organoboranes and organoborates that have been used as selective reducing agents include partially alkylated organobor-

anes, such as 9-BBN (5.157), disiamylborane (5.158), and thexylborane (5.27, 5.159), trialkylboranes, such as B-alkyl-9-BBN's (5.160), partially organo-substituted borates, such as NaBH_3CN (5.161), LiBR_3H and KBR_3H (5.162), and tetraorganoborates, such as lithium dialkyl-9-borabicyclo[3.3.1]nonanes (5.163). Since there are many excellent reviews of these reagents, such as those cited above, a very brief discussion is presented here.

Organoboranes and organoborates may be viewed as modified borane (BH_3) and borohydrides, for example, NaBH_4 , respectively. The effect of an alkyl group in organoboranes appears twofold. Introduction of an alkyl group not only decreases their electrophilicity via inductive effect but also exerts steric hindrance. As a result, partially alkylated organoboranes are generally milder reducing agents than BH_3 itself (5.164), as indicated in Table 5.2. On the other hand, the presence of three or even two electron-donating organic groups in organoborates make them some of the most powerful nucleophiles known to organic chemists, while NaBH_3CN , which contains the electron-withdrawing CN group, is a milder reducing agent than NaBH_4 . In light of the very low nucleophilicity of tetraalkylborates in the intermolecular sense (Sect. 5.2.3.3), the exceedingly high nucleophilicity of trialkylborohydrides might be puzzling. It may be noted that, whereas attack of the B-C bond of organoborates, front or back, by an electrophile appears severely hindered by steric crowding (5.16), the s orbital of the hydrogen atom of the B-H bond of borohydrides does not appear to suffer from similar steric hindrance (5.17). It is even possible that the alkyl groups of organo-substituted borohydrides may exert steric acceleration in addition to their inductive effect mentioned above.



5.16



5.17

As a rough guide, the reducing properties of some representative boranes and borates are summarized in Table 5.2. Some noteworthy reducing properties of organoboranes and organoborates are briefly discussed below.

Thexylborane (5.27, 5.159). Under carefully controlled conditions, thexylborane can reduce free aliphatic and aromatic carboxylic acids to aldehydes.

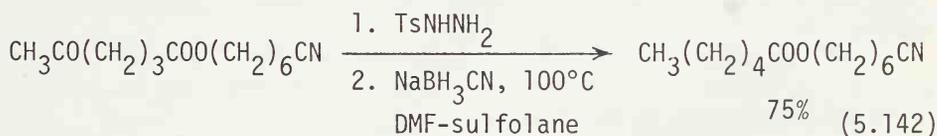
Table 5.2. Selective Reduction with Boranes and Borates

Functional Group	BH ₃ ·THF	Si a ₂ BH	9-BBN	NaBH ₄	MBR ₃ H (M = Li or K)	NaBH ₃ CN Neutral or Basic	NaBH ₃ CN Acidic
Aldehyde	+	+	+	+	+	-	+
Ketone	+	+	+	+	+	-	+
Acid halide	-	-	+	+	+	-	+
Lactone	+	+	+	± (very slow)		-	-
Ester	±	-	+	± (slow)	±	-	-
Epoxide	+	± (slow)	+	± (very slow)	+	-	+
Carboxylic acid	+	react but no reduction	± (very slow)	react but no reduction		-	-
Carboxylic acid salt	-	-	-	-	-	-	-
<i>t</i> -Amide	+	+	+	-		-	-
Nitrile	+	± (very slow)	+	-		-	-
Nitro	-	± (very slow)	-	-	-	-	-
Olefin	+	+	+	-	±	-	-

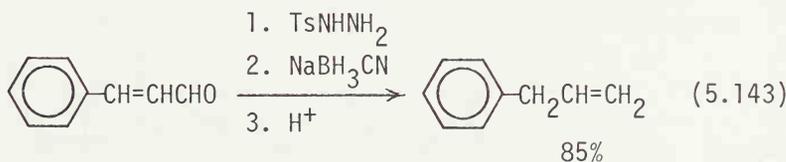
Disiamylborane (5.158). Lactones can be reduced to hydroxyaldehydes with one mole of disiamylborane. Similarly, tertiary amides can be reduced to aldehydes. In many cases, however, the same transformations can also be achieved with diisobutylaluminum hydride (DIBAH); see Sect. 5.3.3.3. Disiamylborane can also be used to protect free carboxylic acids.

9-BBN (5.157). Quite unexpectedly, 9-BBN reduces acyl chlorides relatively rapidly. Another somewhat unexpected finding is the reduction of conjugated enones to allylic alcohols with one mole of 9-BBN (5.165). Although many other reducing agents can also be used for this transformation, 9-BBN ranks among the best along with DIBAH (Sect. 5.3.3.3).

NaBH₃CN (5.161). One of the most unique features of NaBH₃CN is that it is reasonably stable in aq acidic media. Under neutral or weakly basic conditions, practically all electrophiles, except alkyl halides and sulfonates (5.166), are inert. As a reagent for the reduction of alkyl halides, however, NaBH₃CN is generally inferior to trialkylborohydrides. Under acidic conditions, a wide variety of functional groups can be reduced. The reductive amination of aldehydes and ketones with NaBH₃CN represents one of the best methods for converting them into amines. Oximes and enamines can be reduced to *N*-alkylhydroxylamines and tertiary amines, respectively (5.167). Treatment of aliphatic ketone and aldehyde tosylhydrazones with NaBH₃CN in acidic DMF-sulfolane provides a selective and high-yield method for deoxygenation of aldehydes and ketones; see eq. 5.142 (5.168).

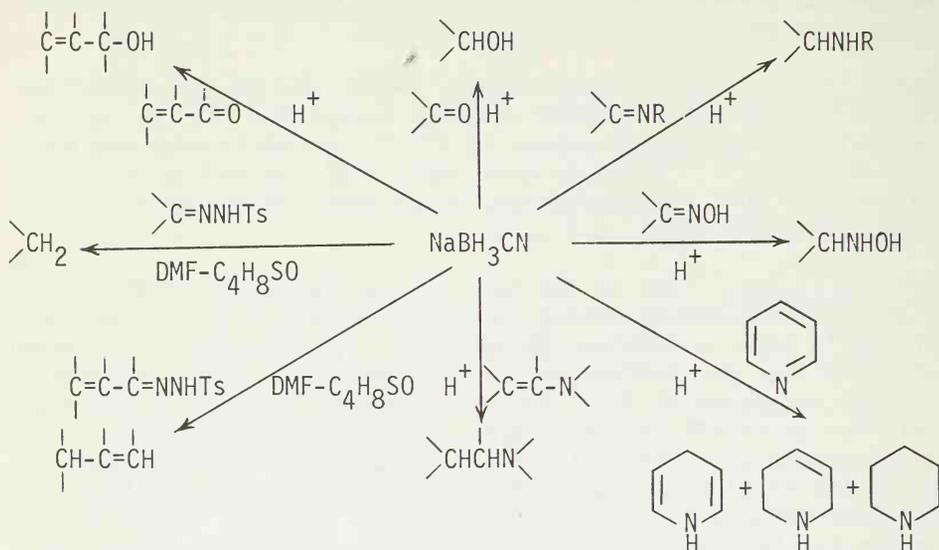


This reaction represents a useful alternative to the Wolff-Kishner reduction. The reduction of α,β -unsaturated aldehydes and ketones by this procedure is accompanied by complete allylic rearrangement, for example, eq. 5.143 (5.169).



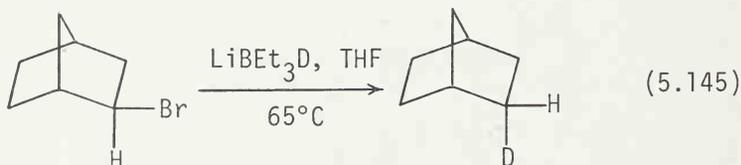
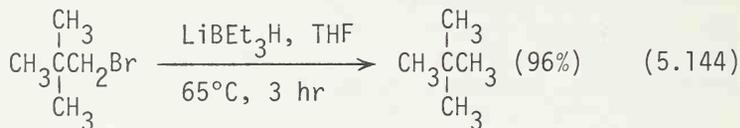
Some of the unique reducing capabilities of NaBH_3CN are summarized below.

Scheme 5.10

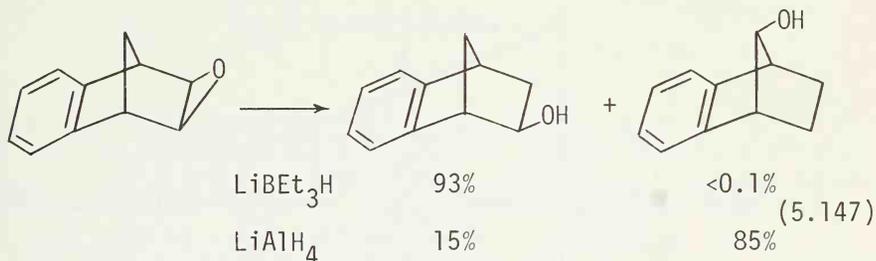
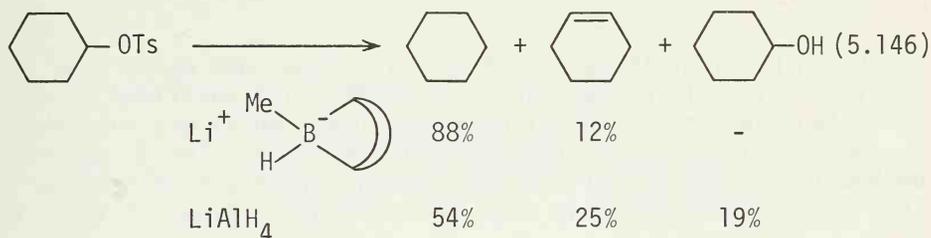


Trialkylborohydrides (5.162). Trialkylborohydrides have exhibited exceptional synthetic capabilities in the reduction of four types of organic compounds, that is, (1) alkyl halides and sulfonates (5.170), (2) epoxides and other strained cyclic ethers (5.171), (3) aldehydes and ketones (5.172), and (4) conjugated enones (5.173).

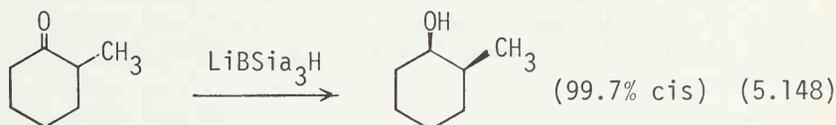
The reduction of primary and secondary alkyl halides can most efficiently be achieved with trialkylborohydrides (5.170). Some noteworthy examples follow.

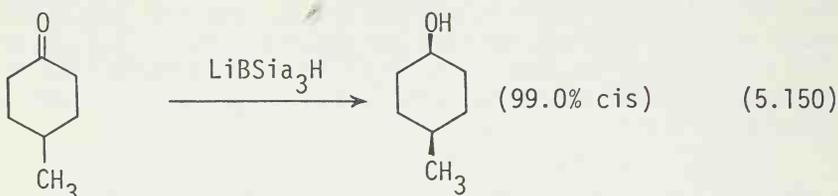
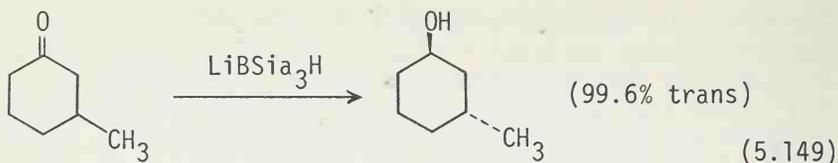


The available data indicate that the reaction is of the S_N2 type. The exceptional nucleophilicity of trialkylborohydrides may be indicated by the following second-order rate constants ($l \text{ mole}^{-1} \text{ min}^{-1}$) for the reaction of various nucleophiles with *n*-octyl chloride in THF at 25°C (5.170): LiEt_3BH (2×10^{-1}), NaSPH (1×10^{-2}), LiAlH_4 (5×10^{-3}), and LiBH_4 (2×10^{-5}). Although trialkylborohydrides are inert to aryl halides, they can be activated toward aryl and alkenyl halides by the addition of CuI (5.174). The exceptional nucleophilicity of trialkylborohydrides is also evident in their reactions with alkyl tosylates (5.170b) and with epoxides (5.171).

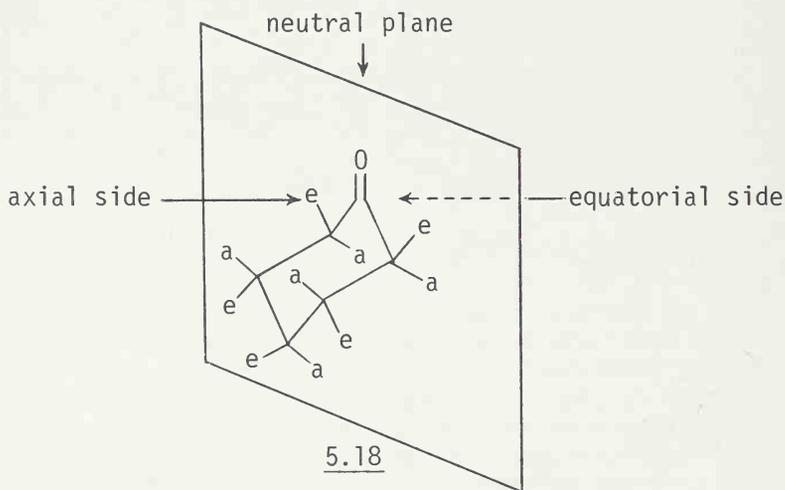


One of the most remarkable properties of trialkylborohydrides is their unprecedented ability to reduce ketones selectively and consistently from the less hindered side of the carbonyl group (5.172). Although some trialkylborohydrides of complex structure were used in earlier studies (5.172a, 5.172b), steric hindrance appears to be the single most important factor. Lithium trisiamylborohydride (5.172e) is probably the most stereoselective nonenzymatic reagent for the reduction of ketones.

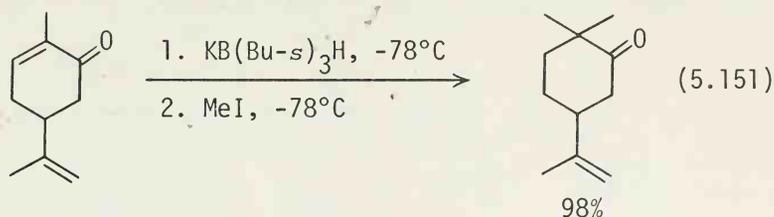




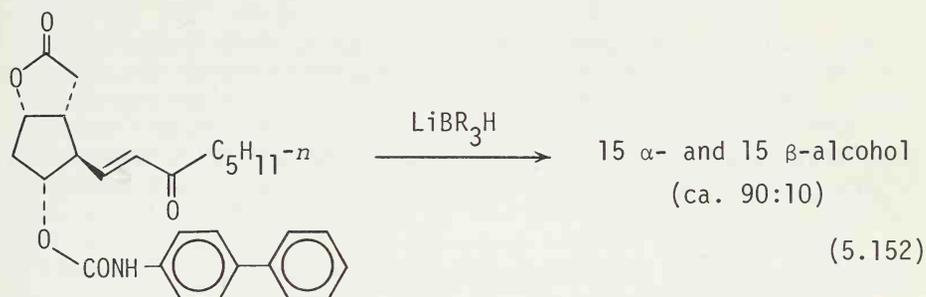
It should be clear that, except in rare situations where some bulky substituents occupy the 2- and/or 6-axial positions, the so-called equatorial side of cyclohexanones, which has only the 2- and 6-axial groups, is the less hindered side. The 2- and 6-equatorial groups as well as the carbonyl group are in the neutral plane, and everything else is on the axial side, as shown in 5.18.



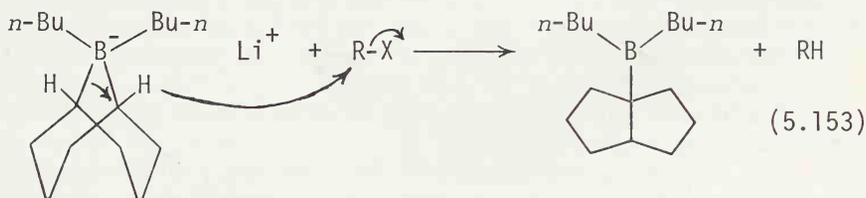
Trialkylborohydrides tend to undergo conjugate reduction of enones to form the corresponding regio-specified enolate which can be alkylated regiospecifically, for example, eq. 5.151 (5.173b).



In some cases where the β -carbon atom of enones is relatively hindered, the carbonyl group has been reduced, for example, eq. 5.152 (5.173a).

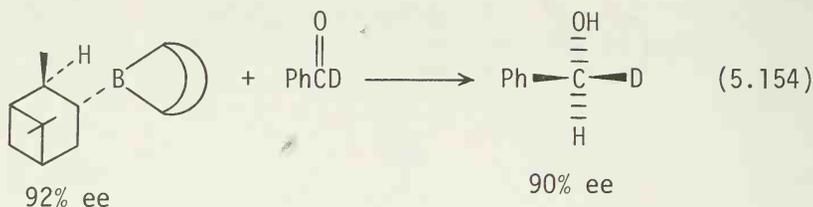


Lithium Dialkyl-9-borabicyclo[3.3.1]nonanates (5.163). Lithium di-*n*-butyl-9-borabicyclo[3.3.1]nonanate reduces tertiary alkyl, benzylic, and allylic halides without reducing primary and secondary alkyl halides (5.175). It is one of the bridge-head hydrogens that acts as a hydride (eq. 5.153). Aldehydes, ketones, and epoxides can also be reduced (5.176).



B-Alkyl-9-BBNs (5.160). B-Alkyl-9-BBNs having tertiary C-H bonds in the β -position, for example, B-(2-methylcyclopentyl)-9-BBN reduces aldehydes at 65°C (5.160). Benzyl- α -d alcohol of 90% enantiomeric excess has been obtained using B- α -pinanyl-9-BBN of 92%

enantiomeric excess; see eq. 5.154 (5.160b).



5.3 ORGANOALUMINUMS

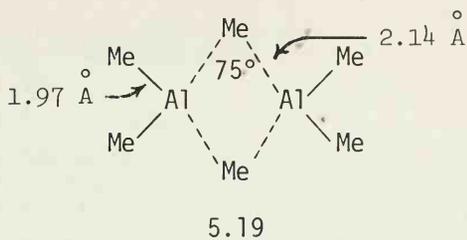
In addition to a few general treatises (0.6, 0.8) that discuss the chemistry of organoaluminums established through the mid-1960s, there is an extensive monograph on organoaluminum chemistry published in 1972 (5.177). An extensive review in German is also presented in Houben-Weyl (5.178). The synthetic aspects of organoaluminums have been reviewed by Bruno (5.179), Reinheckel (5.180), and Negishi (5.36).

5.3.1 Fundamental Properties of the Aluminum Atom and Organoaluminum Compounds

Aluminum lies immediately below boron in the Periodic Table and has the electronic configuration: $3s^2 3p$. As might be expected, these two elements display similar properties. One of the most significant properties common to both of these elements is their ability to form Lewis-acidic sextet species as stable compounds that have an empty p orbital available for coordination. Such sextet species, which may exist as dimeric or polymeric aggregates, are called alanes, regardless of their degree of aggregation. Many of the reaction characteristics of organoboranes associated with the availability of the empty p orbital are also found in organoalanes.

There are, however, a number of significant differences which must be emphasized here.

The Allred-Rochow (1.8) and Pauling (1.1) electronegativity values for aluminum are 1.47 and 1.61, respectively, which are roughly 0.5 lower than the corresponding values for boron. Thus the Al-C bond is considerably more ionic than the corresponding B-C bond. Moreover, the former is considerably longer and more polarizable than the latter. For example, the Al-C bond lengths of Me_3Al , which exists as a bridged dimer 5.19, are 1.97 and 2.14 Å (5.181). The B-C bond length of Me_3B is 1.57 Å.



These properties combine to make organoaluminums better carbanion sources than the corresponding organoboranes. Indeed, it has long been known that organoalanes undergo Grignard-like reactions, that is, intermolecular transfer reactions, with a variety of organic and inorganic electrophiles. As will become clear from the discussions presented later in this chapter, the intermolecular transfer is the predominant mode of reaction of organoaluminums.

There are, however, some significant differences between the intermolecular transfer reactions of organoaluminums and those of Grignard reagents or organolithiums. Just recall the case of cross coupling (Sect. 4.3.2.1). The order of reactivity of alkyl halides toward the highly basic organometallics is: primary > secondary > tertiary. Moreover, hindered alkyl halides undergo mainly β -elimination reactions. On the other hand, the order of reactivity of alkyl halides toward organoalanes is: tertiary > secondary > primary. In fact, typical primary alkyl halides, such as ethyl iodide, are quite inert, indicating that the intrinsic nucleophilicity of the Al-C bond of organoalanes is rather low. These results indicate that the reaction of Grignard reagents and organolithiums is essentially associative or S_N2 -like, whereas that of organoalanes is dissociative or S_N1 -like. Complexation between organoalanes with alkyl halides, in which the organoalanes act as electrophiles, must be a crucial step of the cross-coupling reaction of organoalanes, and appears far more significant than in the corresponding reaction of Grignard reagents and organolithiums. The effect of complexation seems two-fold or synergistic. It should increase not only the electrophilicity of the alkyl group of alkyl halides through polarization or ionization, but also the nucleophilicity of the Al-C bond by weakening it electronically and sterically and making the bonding electrons more readily available for interaction with electrophiles. This point is further elaborated later.

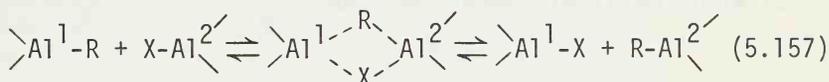
Alanes react with various bases to form the corresponding octet species called aluminate or alamate anions as shown in eq. 5.155.

5.3.2 Preparation of Organoaluminums

5.3.2.1 Preparation of Organoalanes

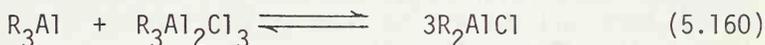
Oxidative metallation (Method I), hydrometallation (Method VI), and transmetallation (Method XI) represent three general methods for preparing organoaluminums. Before discussing these reactions, however, some of the general organoalane reactions which convert one organoalane into another are discussed briefly.

Disproportionation. Organoalanes are considerably more reactive with respect to disproportionation than the corresponding organoboranes.



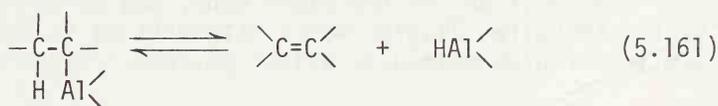
X = C, N, O, or halogen group

Typical examples follow.



The disproportionation reaction often takes place even under very mild reaction conditions, thereby providing a convenient indirect route to organoalanes. Although it can also represent a problem, the overall structural integrity of organoalanes has seldom been critical in organic synthesis. Consequently, disproportionation is usually not a deleterious factor.

Dissociation and Displacement. Organoalanes are considerably more labile than organoboranes with respect to dissociation into olefins and aluminum hydrides. In fact, it is difficult to prepare pure trialkylalanes uncontaminated with dialkylalanes from di- and polysubstituted olefins. Dissociation must involve the precise reversal of hydroalumination.

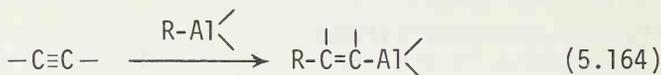
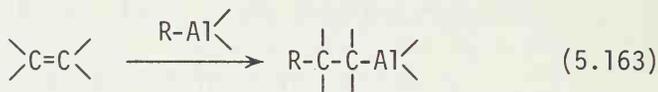


If an unhindered olefin is present in the reaction mixture undergoing dissociation, it can react with the aluminum hydride generated via dissociation. The overall transformation involves displacement of one olefin with another that can form the more stable organoalane of the two.

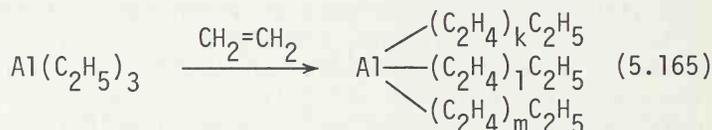
The displacement reaction provides a useful method for the synthesis of certain organoalanes; see eq. 5.162 (5.183).



Carboalumination. At elevated temperatures, organoalanes can also undergo addition reactions with olefins, acetylenes, dienes, and polyenes (5.184). The reaction often takes place in competition with the displacement reaction.



In cases where the organoalane products possess reactivities comparable to those of the starting organoalanes, polymerization involving multiple carbometallation takes place. Thus, for example, ethylene reacts with Et_3Al and $n\text{-Pr}_3\text{Al}$, but not with Me_3Al , at 90 to 120°C and 100 atm to form trialkylalanes containing long linear alkyl groups (5.185).



The chain length of the alkyl groups is a function of various factors. At 100 atm, the alkyl chain grows to about C_{200} and is detached as a long chain olefin via displacement.

The polymerization reaction can produce trialkylalanes containing C_4 to C_{30} linear alkyl groups by controlling the ratio of ethylene to Et_3Al . Controlled oxidation of the products produces, after hydrolysis, primary alcohols.

The reaction, on the other hand, can be markedly facilitated by the so-called Ziegler-Natta catalysts so as to produce polyolefins of high molecular weight (5.186). Since this reaction

involves the use of transition metal compounds, it is discussed later in more detail (Sect. 10.2).

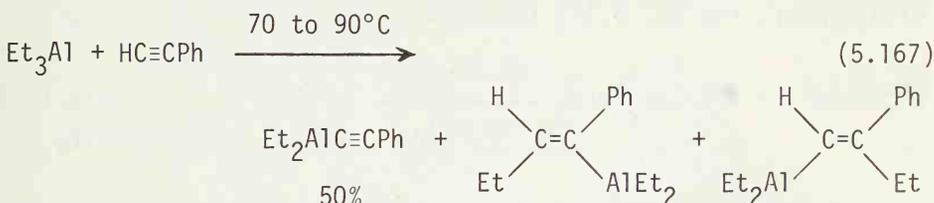
Carboalumination of olefins is probably of little significance as a method for preparing monomeric organic compounds, since it is generally difficult to suppress undesirable side reactions, such as polymerization and displacement. Moreover, there is little incentive to prepare monomeric organic compounds via carboalumination of olefins. On the other hand, carboalumination of acetylenes offers an attractive possibility of synthesizing tri- or tetrasubstituted olefins in a selective manner. Until recently, however, the synthetic scope of carboalumination of acetylenes had been very limited. Some of the more useful examples are shown below.

Acetylene itself reacts with trialkylalanes, such as Et_3Al and $(i\text{-Bu})_3\text{Al}$, to form alkenylalanes (5.167).

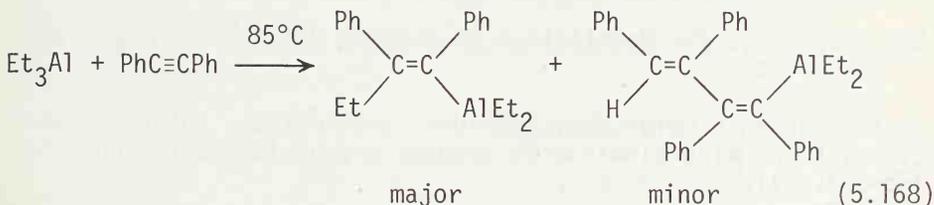


The synthetic utility of the reaction does not appear to have been well delineated.

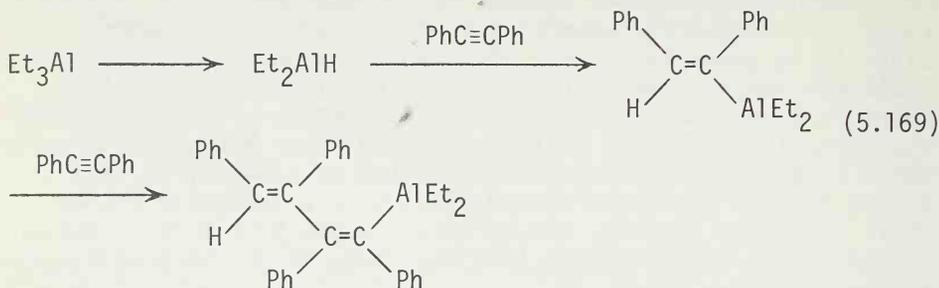
The reaction of organoalanes with monosubstituted acetylenes is usually complicated by (1) metallation of acetylenes and (2) formation of the two possible regioisomers (5.188), as exemplified by the reaction shown in eq. 5.167.



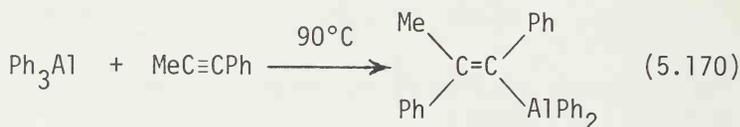
The synthetic utility of the carboalumination of disubstituted acetylenes is severely limited by (1) the lack of high regioselectivity and (2) the competitive dimerization and polymerization. A typical example follows (5.188).



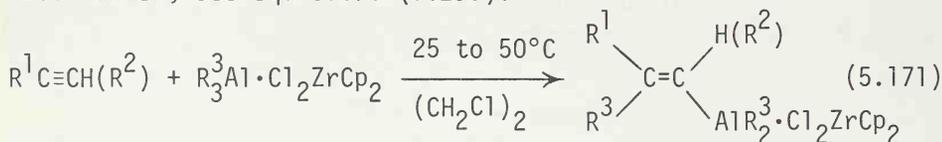
The minor product presumably arises via dissociation, hydroalumination, and carboalumination (eq. 5.169).



Only in some favorable cases is the reaction both regio- and stereoselective (5.189).



Recently, it has been discovered that mono- and disubstituted acetylenes react under very mild conditions with reagents obtained by mixing organoalanes with Cl_2ZrCp_2 to produce the corresponding alkenylmetal derivatives in a highly stereoselective manner; see eq. 5.171 (5.190).

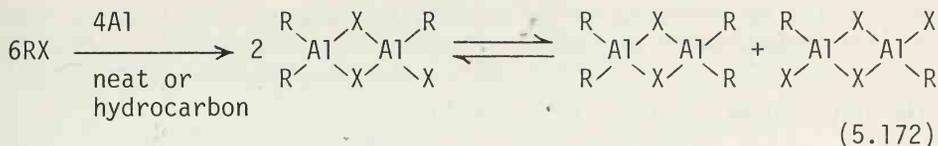


This reaction holds considerable promise as a selective route to tri- and tetrasubstituted olefins, as discussed later in more detail (Sect. 10.2).

It should be kept in mind that the organoalane interconversion reactions discussed above can accompany and complicate the preparation of organoalanes with the reactions discussed below.

5.3.2.2 Oxidative Metallation of Organic Halides with Aluminum Metal

Certain organic chlorides, bromides, and iodides, but not fluorides, react with aluminum to produce organoaluminum sesquihalides (5.191).



The reaction is analogous to the formation of Grignard reagents from organic halides but is of much more limited scope.

Organic halides which have been successfully converted to organoaluminum sesquihalides include: methyl, ethyl, *n*-propyl, allylic, propargylic, and benzylic halides. The reaction represents the most convenient route to organoalanes containing some of these groups. It is difficult to use higher alkyl halides. Phenyl iodide reacts with aluminum at 100°C. Aryl bromides and chlorides are unreactive toward ordinary aluminum metal, although they will probably react with the aluminum vapor and powder discussed earlier (Sect. 2.1).

These organoaluminum sesquihalides are satisfactory reagents in most cases. They can also be converted to mono-, di-, and triorganoalanes, however, via disproportionation.

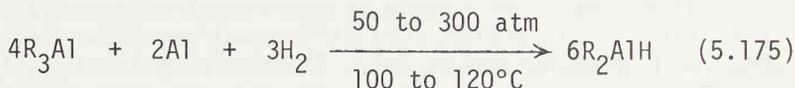
5.3.2.3 Hydroalumination

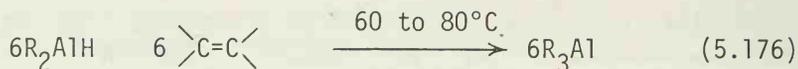
Hydroalumination with Hydroalanes. Certain aluminum hydrides react with olefins and acetylenes to form the addition products (5.187, 5.192).



In most cases, the aluminum hydride reagents used are diorganoaluminum hydrides. Although they can be prepared by the reduction of various organoalanes of the R_2AlX type with saline metal hydrides, such as LiH and NaH, it is the so-called "direct" synthesis that has made certain dialkylaluminum hydrides industrially important chemicals.

The direct synthesis of organoalanes consists of the following two reactions (5.193).





The net change is shown in eq. 5.177.



It is important to note that aluminum metal and hydrogen do not react even under these drastic conditions, unless a trialkylalane is present. The direct synthesis, which is also called the Ziegler synthesis, can be carried out either in one step or two steps. The one-step procedure is, of course, the more desirable of the two. There are, however, at least two side reactions, namely, hydrogenolysis of trialkylalanes and carboalumination of olefins, which must be taken into consideration. Both of these problems can be avoided in the two-step procedure. Triisobutylalane, which does not participate readily in either of the side reactions, is usually prepared by the one-step method, whereas triethylalane requires the two-step procedure.

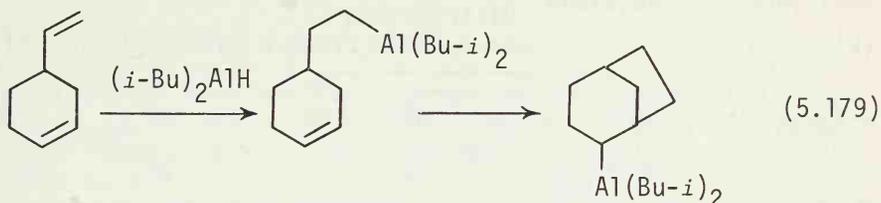
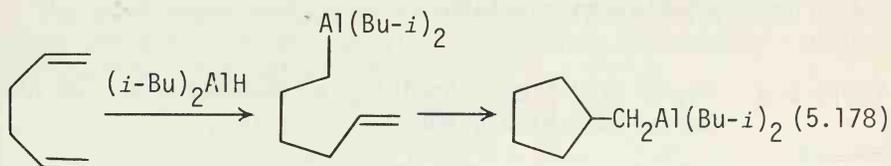
It should also be noticed that typical alkylalanes are remarkably stable to hydrogen. The hydrogenolysis of R_3Al to form R_2AlH can be achieved only at $\geq 120^\circ\text{C}$ and about 300 atm, unless catalyzed by some transition metal compounds.

Scope of Hydroalumination. The scope of hydroalumination of olefins is considerably more limited than that of hydroboration, mainly due to (1) competitive dissociation and displacement and (2) competitive carboalumination. The two hydrometallation reactions, however, share some significant common features. Both reactions involve a cis addition which predominantly proceeds in the anti-Markovnikov sense. It is therefore likely that the mechanisms of the two reactions are also very similar (Sect. 2.6.1).

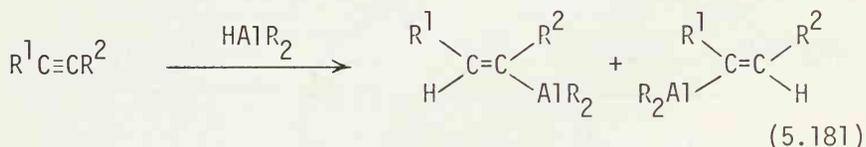
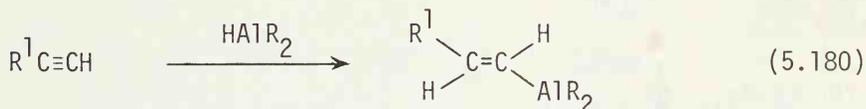
(a) Olefins. The approximate order of reactivity of various types of olefins is: $H_2C=CH_2 > H_2C=CHR > H_2C=CRR' > RCH=CHR'$. Many exceptions exist, however. For example, norbornene is more reactive than 1-hexene. Triisobutylaluminum contains a small amount (~10%) of diisobutylaluminum hydride (DIBAH). It is therefore difficult to prepare by hydroalumination pure trialkylalanes, which are sterically more demanding than *i*-Bu₃Al.

(b) Dienes. The course of hydroalumination of dienes (5.194) is often considerably different from that of the corresponding hydroboration (5.16). The reaction is often followed by

the intramolecular carboalumination, which provides an attractive method of forming carbocyclic derivatives, as shown in the following examples, see eqs. 5.178, 5.179 (5.195).



(c) Acetylenes. Hydroalumination of acetylenes has proven to be of considerable synthetic interest in recent years, although its scope is much more limited than that of hydroboration. Under carefully controlled conditions, usually at about 50°C, dialkylaluminum hydrides react with acetylenes to give 1:1 cis-addition products (5.187, 5.196).



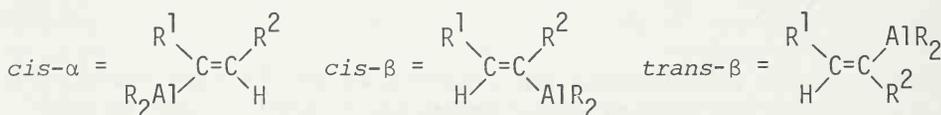
The reaction can, however, be complicated by (1) substitution of the methine hydrogen or other heterosubstituents, such as bromine and SnR_3 , and (2) competitive carbometallation. Moreover, the regiochemistry and stereochemistry of hydroalumination of internal acetylenes are often nonselective. The representative results are summarized in Table 5.3.

One of the serious limitations of hydroalumination is its incompatibility with various functional groups. As discussed

later, various functional groups are readily reduced by aluminum hydrides. Even most of the etherial functionalities cannot be tolerated, although they are not usually destroyed. This represents a major disadvantage of hydroalumination in relation to other hydrometallation reactions.

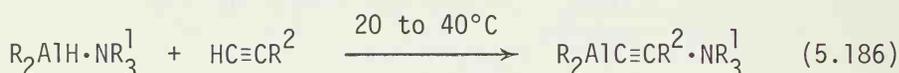
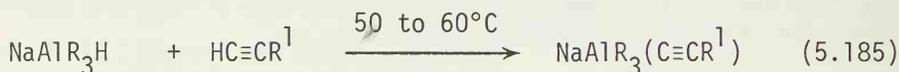
Table 5.3. Regio- and Stereochemistry of Hydroalumination of Acetylenes with DIBAH

Acetylene ($R^1C_\alpha \equiv C_\beta R^2$)	Conditions	Product Distribution (%)			Ref.
		<i>cis</i> - α	<i>cis</i> - β	<i>trans</i> - β	
$n-C_4H_9C \equiv CH$	50°C	2	88	6	5.197
$PhC \equiv CH$	20°C		71	29	5.198
$n-C_4H_9C \equiv CCH_3$	70°C	33	67		5.200
$\text{---}C \equiv CCH_3$	70°C	15	85		5.200
$PhC \equiv CCH_3$	50°C	82	18		5.200
$PhC \equiv C\text{---}$	50°C	100	0		5.199
$PhC \equiv CBr$	100°C			100	5.198
$PhC \equiv CSiMe_3$	{ 60°C, 20°C		96	4	5.198
			4	96	5.198
$PhC \equiv CSnMe_3$	20°C			100	5.198



Hydroalumination with Hydroaluminates. Unlike dialkylalanes (R_2AlH), hydroaluminates, such as $LiAlH_4$ and $LiAl(Bu-i)_2MeH$, react with internal acetylenes to form the (*Z*)-isomers via *trans* addition (5.201).

One of the major limitations of the trans hydroalumination of acetylenes is that the terminal acetylenes cannot be used in this reaction, since their reaction with hydroaluminates produces alkynylaluminates. A similar reaction also occurs with hydroalanes complexed with tertiary amines (5.179).



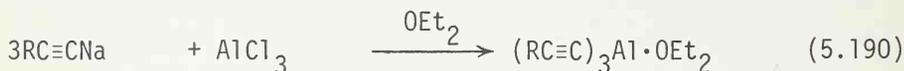
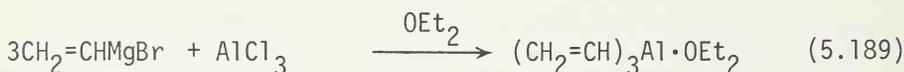
5.3.2.4 Organoalanes via Transmetalation and Organoaluminates via Complexation

Organoalanes that cannot be prepared via oxidative metallation or hydroalumination can most conveniently be prepared by treating organometallics containing alkali metals and magnesium with aluminum halides (eq. 5.187).



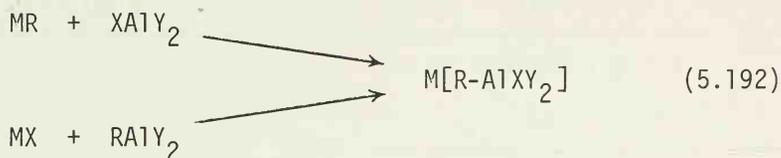
M = Li, Na, K, Mg, and so on

Typical examples are shown below.

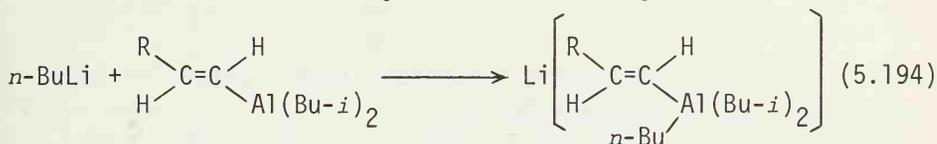


The immediate products of the reaction of alanes with polar organometallics are organoaluminate complexes (MAlRXY_2). If they decompose, organoalanes (RAlY_2) are formed. If they do not, the organoaluminates are obtained as the final products. As in the case of the synthesis of organoborates, this complexation method

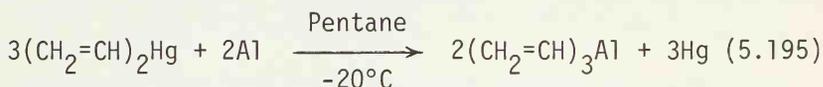
represents by far the most general route to organoaluminates. It is also possible to obtain organoaluminates by treating organoalanes with either organometallics or inorganic salts; see eq. 5.192 (5.204).



A few representative examples are shown below.



Finally, certain ether-free organoalanes can be prepared by treating organomercuries with aluminum metal (Method XII, Sect. 2.12), as in the following synthesis of trivinylalane (5.205).



5.3.3 Reactions of Organoaluminums

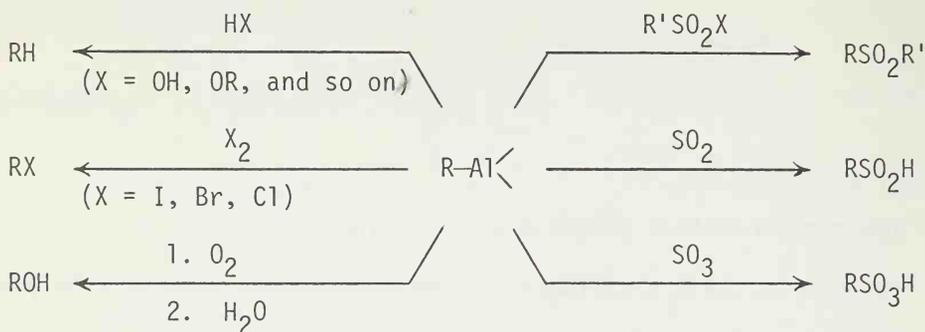
The general patterns of the reactions of organoaluminum compounds are briefly discussed in Sect. 5.3.1. Various specific reactions of organoaluminums of synthetic interest are presented in this section.

5.3.3.1 Formation of Carbon-Hetero Atom Bonds via Organoaluminums

Reactions with Nonmetallic Reagents. The Al-C bond can be cleaved readily with a variety of inorganic reagents to form the corresponding compounds containing the carbon-hetero atom bonds. These reactions represent a convenient and general means of converting organoaluminums into organic compounds. Some of the more

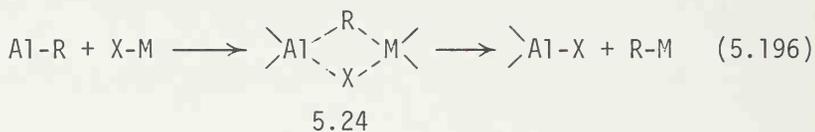
useful transformations are summarized in Scheme 5.11 (5.179).

Scheme 5.11



Under appropriate conditions these reactions provide the indicated products in high yields.

Reactions with Metallic Reagents. The aluminum-containing moiety of organoalanes can also be replaced with various metal-containing groups via transmetalation; see eq. 5.196 (5.206).

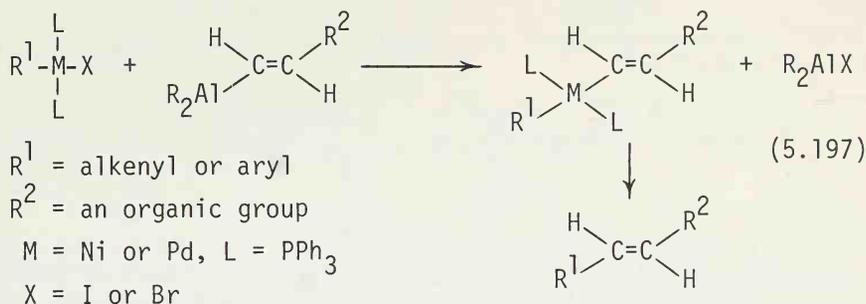


The most noteworthy example of these types of reactions is the formation of an active catalyst in the Ziegler-Natta polymerization reaction, which is believed to be either organotitanium species or Al-Ti complexes represented by 5.24 (M = Ti); see Sect. 10.2.

Organometallics that can be prepared by this method include those that contain Be, Zn, Hg, B, Ga, Si, Sn, Pb, Ti, Zr, Ni, and Ru (5.206). The alkylating ability of organoalanes are, however, generally considerably lower than that of the corresponding alkali metal derivatives. Thus if one is only interested in the preparation of organometallics containing other metals as discrete products, there is little advantage in using organoalanes as starting material over organoalkali metals and Grignard reagents.

The above argument does not apply to the cases where only equilibrium amounts of organometallics are to be generated as intermediates. Recent studies in the author's laboratory indi-

cate that alkenylalanes, readily obtainable via hydroalumination of acetylenes, react with nickel and palladium complexes to form the corresponding alkenyl derivatives of nickel and palladium that undergo reductive elimination to form olefins; see eq. 5.197 (5.207).



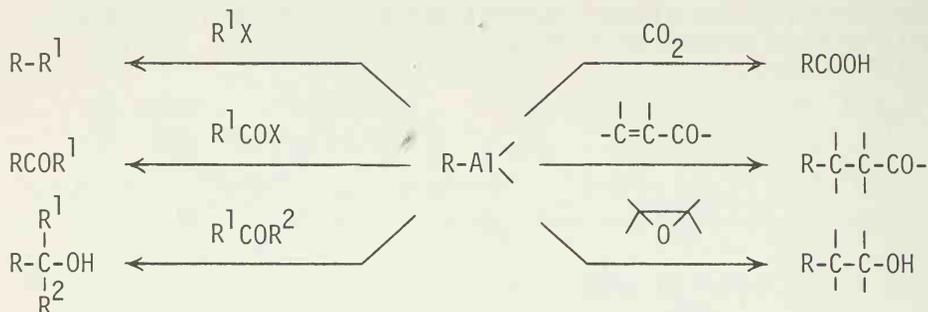
It is important to notice that the preparation of the corresponding alkenyl derivatives of lithium and magnesium is more cumbersome. Moreover, for reasons as yet unclear, the use of organolithiums and Grignard reagents in the nickel- or palladium-catalyzed cross-coupling reaction frequently fails to provide the desired products in high yields. The transmetalations of organoalanes with transition metal compounds is discussed later in greater detail (Sect. 9.2 and 9.3).

5.3.3.2 Carbon-Carbon Bond Formation via Organoaluminums

As discussed earlier, both organoalanes and organoaluminates react with a variety of carbon electrophiles. Organoalanes can act as "amphiphilic" species (species that act as both a nucleophile and an electrophile in a given reaction), and often nicely complement the synthetic capabilities of the nucleophilic organoaluminates.

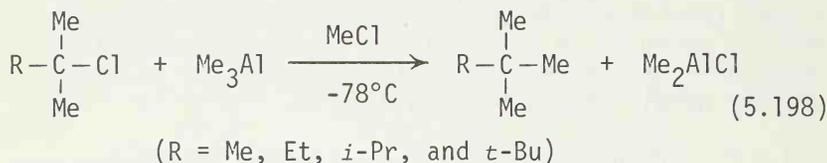
A general scheme for some representative reactions of organoaluminums with carbon electrophiles is shown below. Some of the products often react further. Clearly, organoaluminums act as "Grignard-like" reagents in these reactions, although the mechanistic details and outcomes of these reactions are often unique. Some of the unique features of these reactions are discussed in this section.

Scheme 5.12

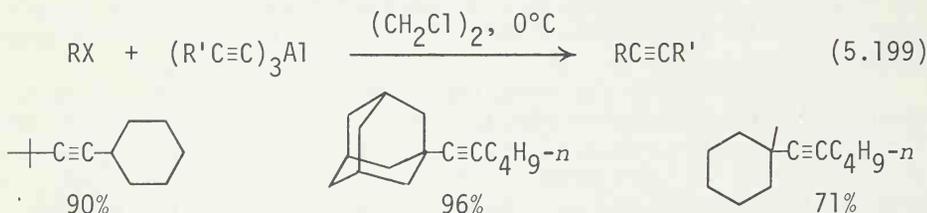


Reactions of Alkyl Halides and Sulfonates. (a) With organoalanes. Typical primary and secondary alkyl halides do not react readily with organoalanes. On the other hand, tertiary alkyl halides and secondary alkyl sulfonates react with certain organoalanes to form cross-coupled products (5.208).

A few synthetically useful examples are shown below (5.209).

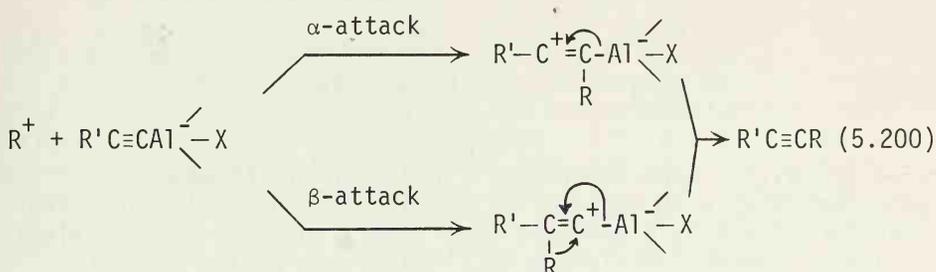


Particularly noteworthy is the reaction of alkynylalanes with tertiary alkyl halides and secondary alkyl sulfonates, which permits a clean *t*-alkyl-alkynyl coupling (5.210).



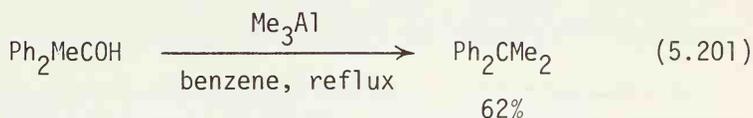
The corresponding reaction of alkenylalanes has been practical only with secondary alkyl sulfonates. The reaction, however, is complicated by (1) stereochemical scrambling and (2) rearrangement of the secondary alkyl group to form a tertiary alkyl group, when possible. The reaction most probably involves ionization of

the alkyl sulfonate to form an ion pair as a transient species. These results suggest the following addition-elimination path for the related alkyl-alkynyl coupling reaction.

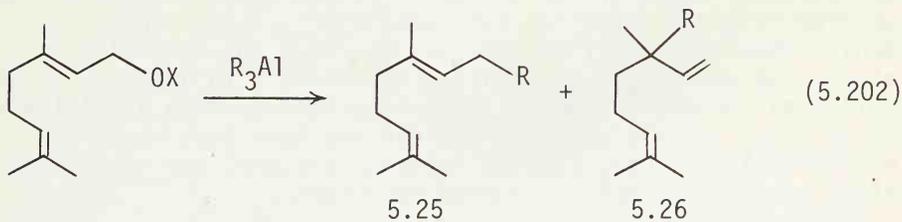


In any event, the ability of organoalanes to undergo coupling reactions with hindered alkyl halides appears to exceed that of any other organometallics. This area clearly deserves further exploration.

Organoalanes also react with certain alcohols and their derivatives other than sulfonates. The reaction of tertiary alcohols requires high temperatures (80 to 200°C), and its scope with respect to the structure of organoalanes appears limited (5.211).



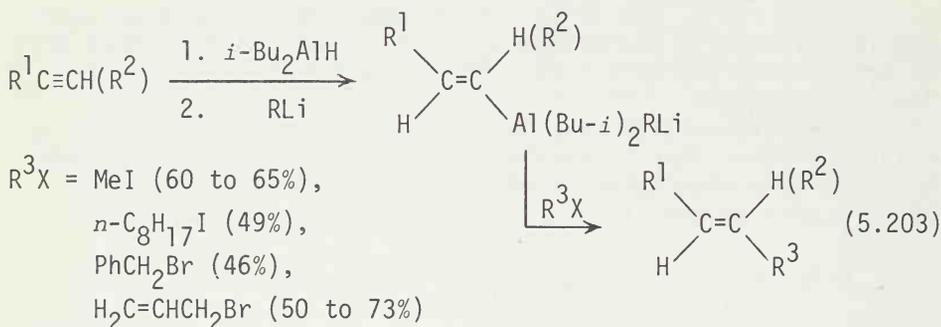
Various derivatives of allylic alcohols react readily with organoalanes, providing a promising procedure for allyl-alkyl coupling; see eq. 5.202 (5.212).



X	R	Total Yield, %	<u>5.25</u> : <u>5.26</u>
P(O)(OEt) ₂	Me	>90	90 : 10
Ac	Me	74	92 : 8

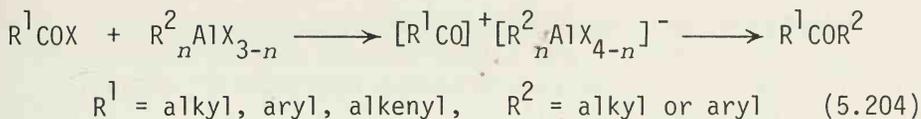
Ac	Bu- <i>i</i>	66	97	:	3
CO ₂ Et	Bu- <i>i</i>	73	97	:	3
OTHP	Me	80	96	:	4
OTHP	Bu- <i>i</i>	3		-	

(b) With organoaluminates. The scope of the reaction of organoaluminates with organic halides appears quite limited. The reaction of alkenylaluminates with highly reactive primary alkyl halides, however, provides a facile stereoselective route to trans-disubstituted olefins; see eq. 5.203 (5.213).



Reactions of Carbonyl Compounds. Just as organolithiums and Grignard reagents do, organoaluminums can participate in (1) alkylation, (2) reduction, and (3) enolization of various carbonyl compounds, such as aldehydes, ketones, carboxylic acids and their derivatives, and nitriles (5.214). In addition, organoaluminums undergo conjugate addition reactions with α,β -unsaturated carbonyl compounds. In this section, we focus our attention on the alkylation and conjugate addition reactions. In general, trialkylalanes possess a greater alkylating ability than alkylaluminum halides. Alkylaluminum alkoxides are even less reactive. Branched alkylalanes, such as triisobutylalane, are poor alkylating agents, and mostly undergo reduction.

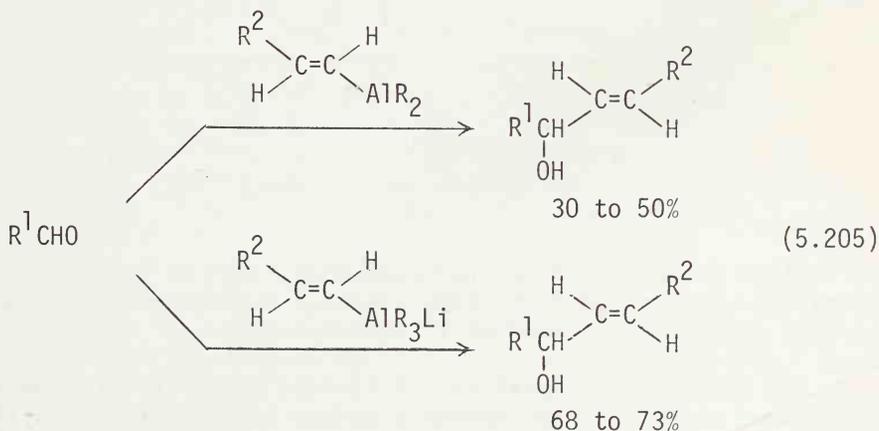
(a) Reaction of acyl halides. The reaction of acyl halides with organoalanes represents one of the most convenient methods for the synthesis of ketones via acyl halides, along with the related reactions of organometallics containing Cd (Sect. 4.3.2.2), B (Sect. 5.2.3.3), Cu (Sect. 9.5), and Fe (Sect. 11.2).



The reaction presumably proceeds via an acylium ion, as shown in eq. 5.204 (5.215). Thus organoalanes presumably act as "amphiphilic" reagents. Acyl chlorides and monoorganoaluminum dichlorides ($RAICl_2$) are most commonly used. Tri- and diorganoalanes also react, but afford only partial utilization of the organic groups. Moreover, these reagents have a greater tendency to react with the ketone products. The solvent of choice is methylene chloride. Aromatic hydrocarbons have also been used, but they tend to undergo Friedel-Crafts acylation. The reaction of organoalanes with acyl halides is chemoselective and general with respect to acyl halides. The scope of the reaction with respect to organoalanes is not clear, as most of those which have been used are alkylalanes.

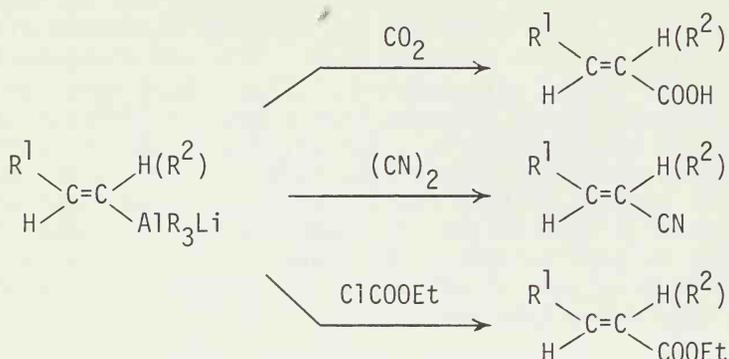
(b) Reactions of aldehydes and ketones. Although organoaluminums can react with these carbonyl compounds to give addition products, these reactions are often complicated by reduction of carbonyl compounds and other side reactions and are generally inferior to the corresponding reactions of organolithiums and other polar organometallics. In some cases, however, organoaluminums offer certain unique advantages, as shown in the following examples.

The reaction of *trans*-alkenylaluminums with aldehydes produces stereodefined allylic alcohols. Organoaluminates (5.216) appear generally superior to the corresponding organoalanes (5.217). These reactions proceed with nearly complete retention of configuration.

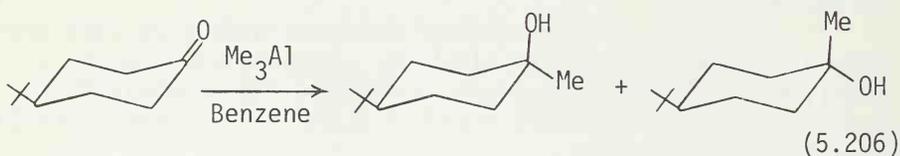


Similarly, the reactions of alkenylaluminates with CO_2 (5.216), $(\text{CN})_2$ (5.218), and ClCOOR (5.219) proceed with retention (Scheme 5.13). The corresponding reactions of alkenylalanes give much poorer results.

Scheme 5.13



The stereochemistry of the reaction of cyclic ketones with organoalanes varies widely depending on the R_3Al /ketone ratio, thereby permitting the formation of certain stereoisomers which are obtainable only as minor products in the corresponding reactions with organolithiums and Grignard reagents (5.220).



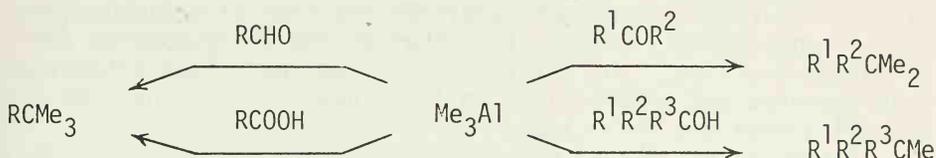
$\text{Me}_3\text{Al}/\text{Ketone}$	Axial	Equatorial
1.0	76	24
2.0	17	83
3.0	12	88

Other carbonyl and related compounds, such as esters and nitriles, cannot readily be alkylated but are readily reduced by various organoalanes, such as triisobutylalane.

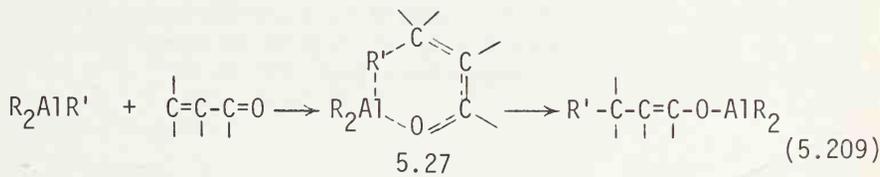
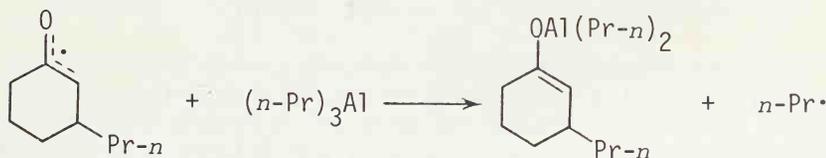
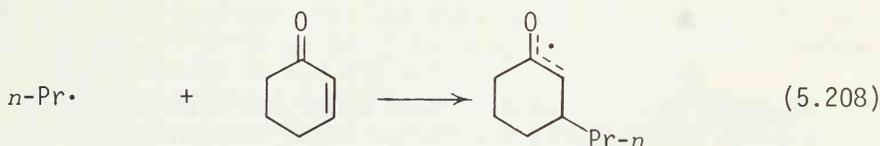
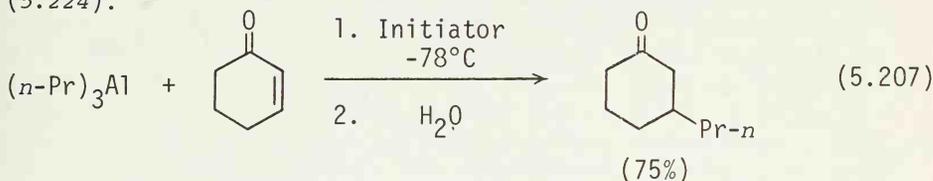
(c) Exhaustive alkylation. A limited number of organoalanes, such as Me_3Al , can undergo a unique exhaustive alkylation

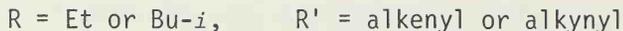
of ketones, aldehydes, carboxylic acids, and carbinols at elevated temperatures of 100 to 200°C (5.221, 5.222).

Scheme 5.14



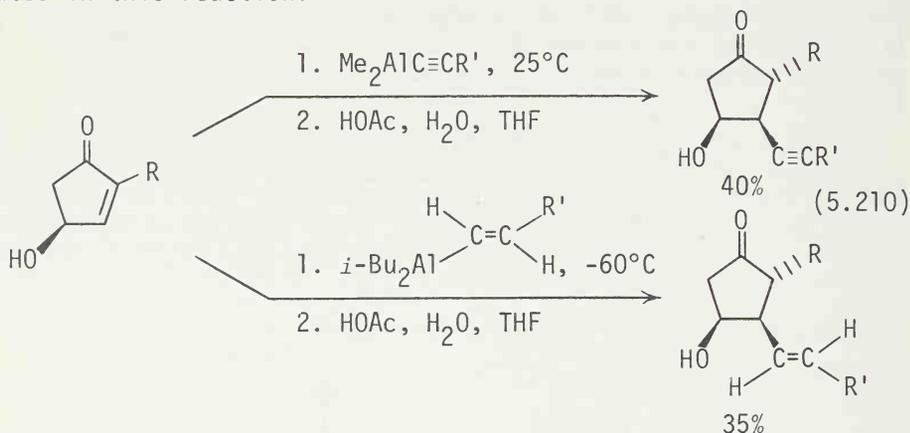
Reactions of α,β -Unsaturated Carbonyl Compounds. (a) With organoalanes. Organoalanes appear to react with conjugated enones by various mechanisms. Some of the reactions appear to proceed by a free-radical mechanism, shown in eq. 5.208 (5.223), as in the corresponding reaction of organoboranes while others occur only when enones can assume the cisoid conformation, indicating the cyclic transition state represented by 5.27; see eq. 5.209 (5.224).





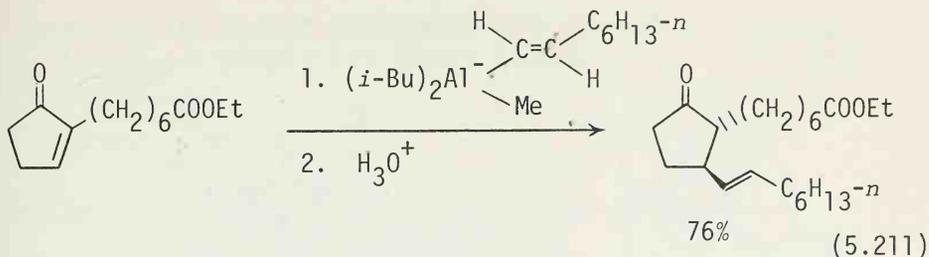
These results closely parallel those obtained more recently with alkenyl- and alkynyl-9-BBNs (Sect. 5.2.3.3). However, the scope of the free-radical conjugate addition reaction of organoboranes appears considerably broader than that of the corresponding organoalane reaction. The relative advantages and disadvantages of organoboranes and organoalanes in the transfer of alkenyl and alkynyl groups are less clear.

Although the alkenyl and alkynyl transfer reaction of organoalanes fails with simple transoid enones, such as cyclohexenone, producing only the 1,2-addition products, certain suitably functionalized transoid enones evidently react via 1,4-addition, as shown in eq. 5.210 (5.225). The stereochemistry of the products strongly suggests that the hydroxy group actively participates in this reaction.



The reaction of organoalanes, such as Me_3Al , with enones can also be markedly catalyzed by transition metal compounds, such as $\text{Ni}(\text{acac})_2$, although the synthetic utility of the nickel-catalyzed reaction has not been well delineated (5.226).

(b) With organoaluminates. Certain transoid enones undergo a conjugate addition reaction with alkenylaluminates; see eq. 5.211 (5.227). No 1,2-addition product is formed. On the other hand, the corresponding reaction of alkenylalanes gives only the 1,2-products. These results should be carefully contrasted with those in eq. 5.210. Unfortunately, little is known about the mechanistic details of these reactions.



(c) The Nagata hydrocyanation reaction. The most extensively developed conjugate addition reaction of organoalanes by far is that of dialkylcyanoalanes, such as Et_2AlCN , discovered and developed by Nagata; see eq. 5.212 (5.228).

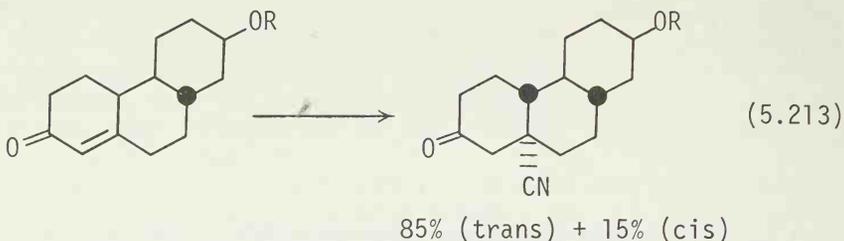


Although the reaction is restricted to the introduction of the cyano group, it is as general as the conjugate addition reaction of organocuprates (Sect. 9.4) with respect to the structure of enones. The required reagent, for example, Et_2AlCN , may be either preformed or generated in situ by the reaction of RAlX_2 with HCN. The reaction is carried out in either hydrocarbons, such as toluene, or ethers, such as THF and dioxane, the reaction rate being considerably faster in toluene than in THF. Although the use of HCN is somewhat inconvenient, the observed results are generally far superior to those observed in other conventional hydrocyanation reactions that use more ionic metal cyanides, such as KCN, which are often complicated by (1) base-catalyzed condensation, (2) hydrolysis, and (3) solvent participation.

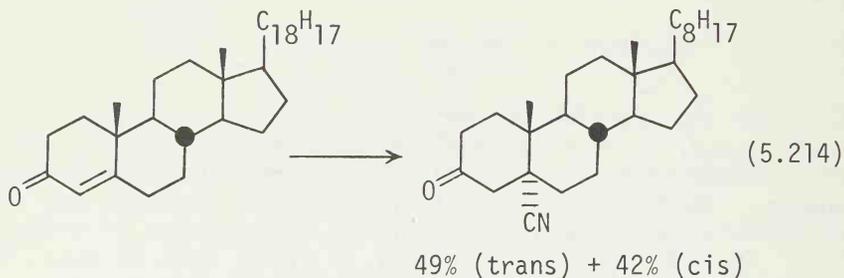
The precise mechanism of the Nagata hydrocyanation is unclear. At least in some cases, however, the kinetically favored products are the 1,2-adducts which subsequently isomerize to give the 1,4-adducts. It is therefore likely that the successful formation of the 1,4-adducts largely, if not entirely, rests on the following. Firstly, the 1,4-adducts are thermodynamically more stable than the corresponding 1,2-adducts. Secondly, the reversal of the 1,2-adduct formation is facile under the reaction conditions.

The stereochemistry of the reaction is somewhat difficult to predict, although, in most cases, the predominant isomer appears to be the one that is the more stable of the two. The following examples (5.228) may be of help in predicting the stereochemistry of a given reaction.

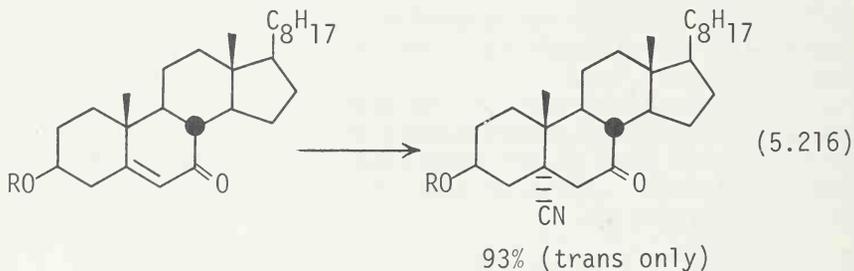
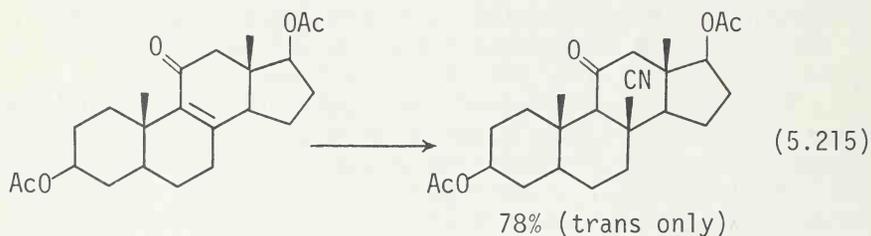
1. Polycyclic octalenones with a terminal ring enone \longrightarrow
trans + cis (trans > cis)



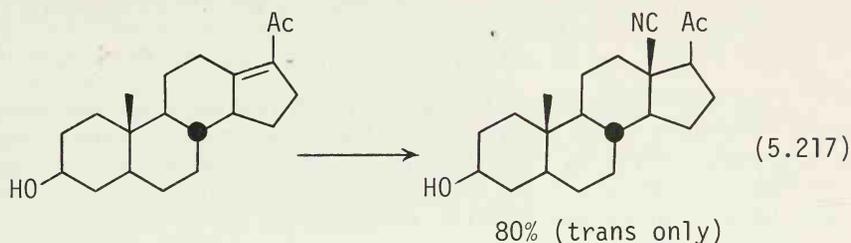
2. Polycyclic methyloctalenones with a terminal ring enone
 \longrightarrow trans + cis (trans \geq cis)



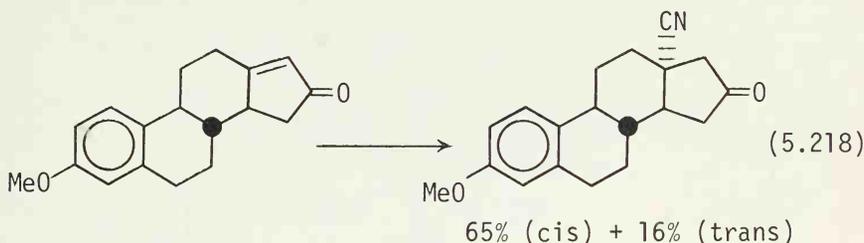
3. Polycyclic compounds with a trans-fused internal enone
 \longrightarrow trans



4. Polycyclic acetylhydrindenes
 \longrightarrow trans + cis (trans \gg cis)

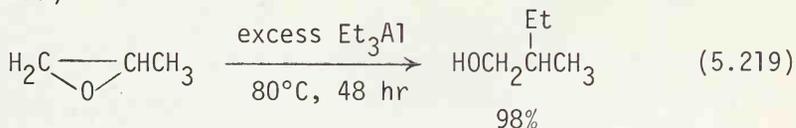


5. Polycyclic hydrindeneones
 \longrightarrow trans + cis (cis \gg trans)



Reactions of Epoxides. While organolithiums (Sect. 4.3.2.3) and organocoppers (Sect. 9.5) remain the two most useful classes of organometallic reagents in the reaction with epoxides, organoaluminums have exhibited some unique synthetic capabilities.

The reaction of sterically unhindered epoxides with organoalanes tends to be complicated by (1) polymerization of epoxides, (2) formation of the two possible regioisomers, and (3) reductive opening of epoxides, although it can lead to the formation of the Markovnikov products in high yields as shown in the following examples (5.179).



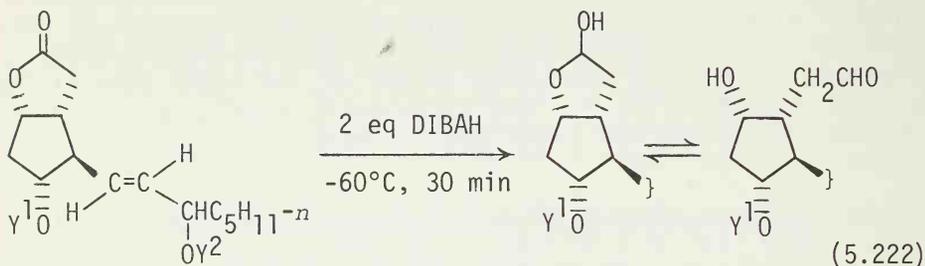
On the other hand, their reaction with organoaluminates cleanly gives the anti-Markovnikov products (5.299). The unique advantage of the use of readily obtainable *trans*-alkenylaluminates should be noted (eq. 5.220). Unfortunately, however, hindered epoxides, such as cyclohexene oxide, do not react readily with organoaluminates.

By far the most widely used organoaluminum reducing agent is (*i*-Bu)₂AlH (DIBAH). While the use of nonhydridic organoaluminums, such as (*i*-Bu)₃Al, might be advantageous in some special cases, such examples seem rare. As yet, relatively little is known about the unique capabilities of the organo-substituted complex aluminum hydrides. Consequently, our discussion in this section is restricted to some of the unique reducing capabilities of DIBAH. Its reaction with olefins and acetylenes is discussed in Sect. 5.3.2.3. Some representative results of the reduction with DIBAH are summarized in Table 5.4.

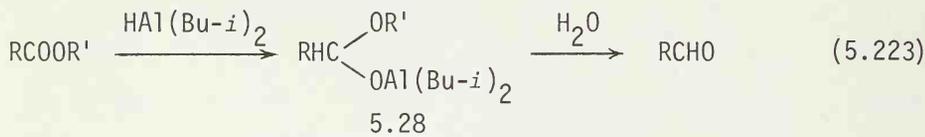
Table 5.4. Reduction of Organic Compounds with DIBAH (5.179)

Organic Compound	Amount of DIBAH (eq)	Product	Typical Yields (%)
RCHO	1	RCH ₂ OH	High
RR'CO	1	RR'CHOH	High
RCOOH	1.35	RCHO	40 to 70
	2.35	RCH ₂ OH	60 to 90
RCOOR'	1	RCHO	70 to 90
	2	RCH ₂ OH	70 to 100
RCOCl	2	RCH ₂ OH	60 to 70
RC(OR') ₃	1	RCH(OR') ₂	90 to 95
RCONR'R''	2 to 3	RCH ₂ NR'R''	75 to 95
RCONHR'	3 to 4	RCH ₂ NHR'	65 to 95
RCN	1	RCHO	80 to 95
	2	RCH ₂ NH ₂	60 to 90
RCH=NR'	1	RCH ₂ NHR'	70 to 95
R- 	1	R(CH ₂) ₂ OH and RCH(OH)CH ₃	High

The following transformations are usually best carried out with DIBAH. Carboxylic acids, esters, lactones, and nitriles are readily converted to aldehydes with DIBAH, as exemplified by the following; see eq. 5.222 (5.232).



The observed success presumably depends on the relatively high stability of the reduction product 5.28 which does not readily decompose to the corresponding aldehyde in the reduction step, but can readily be hydrolyzed to form the aldehyde (eq. 5.223).



Selective reduction of carbonyl compounds and nitriles in the presence of olefins, conjugated or isolated, can readily be achieved with DIBAH as shown in the following example (eq. 5.224) (5.179).



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6

ORGANOSILICONS AND ORGANOTINS (Silicon, Tin)

There are numerous monographs and reviews on the chemistry of organometallics that contain the Group IVA elements. In addition to a textbook by Coates and Wade (0.6), a two-volume treatise edited by MacDiarmid (6.1) provides extensive general coverage of the chemistry of organometallics of the Group IVA elements. A few excellent monographs on organosilicons (6.2) and organotins (6.3 to 6.5) discussing all aspects of these compounds are available. Unfortunately, applications of these organometallics to organic synthesis have been developed mainly after the publication of these monographs. There have been a number of reviews, however, discussing recent results, which are cited throughout this chapter. A series of reviews on recent advances in organosilicon chemistry have appeared in *Pure Appl. Chem.*, 13 (1969); 19 (1969), *Intra-Sci. Chem. Rep.*, 7 (1973), and *J. Organometal. Chem. Libr.*, 2, (1976). New chemistry and applications of organotins have been extensively reviewed by various workers (6.5a).

6.1 SOME FUNDAMENTAL PROPERTIES OF SILICON AND TIN AND THE BONDS TO THESE ELEMENTS

Silicon (Si), germanium (Ge), tin (Sn), and lead (Pb) lie directly below carbon in the Periodic Table (Group IVA elements). As might be expected, the structure and reactivity of organometallics containing these elements are similar in many respects to those of the corresponding carbon compounds. In this book, however, we are mainly interested in the differences between these elements and carbon and some of the unique physical and chemical properties of organometallics containing these elements.

The chemistry of organogermanium compounds is not discussed in this book, since these compounds have not yet found many ap-

plications in organic synthesis. This must be, at least in part, due to the fact that germanium-containing compounds are considerably (10 to $10^2\times$) more expensive than the corresponding silicon and tin compounds. While organolead compounds share many noteworthy properties with the corresponding silicon and tin compounds, they also exhibit chemical properties common to some other organometallics containing heavy elements, such as mercury and thallium. Therefore, their chemistry is discussed in the following chapter along with that of organomercuries and organothalliums.

6.1.1 Electronegativity and Bond Energy

As shown in Table 6.1, the Group IVA elements are characterized by their relatively high electronegativity values, although they are more electropositive than carbon.

Table 6.1 Electronegativity of the Group IVA Elements

Element	Electronegativity	
	Pauling (1.1)	Allred-Rochew (1.8)
C	2.5	2.60
Si	1.8	1.90
Ge	1.8	2.00
Sn	1.8	1.93
Pb	1.8	2.45

Thus their bonds to carbon and hydrogen are highly covalent. The covalent radii for silicon and tin are 1.17 and 1.40 Å, respectively, and are reasonably independent of the nature of the ligands bonded to these metals. Due to their highly covalent nature, the intrinsic nucleophilicity of the Si-C and Si-H bond is low. Direct cleavage of the Si-C bond seldom takes place in the reaction of organosilicons with electrophiles, although certain functionalized organosilicons, such as α,β -unsaturated derivatives, can react with electrophiles by multistep mechanisms, as discussed later. On the other hand, the Sn-C bond, although highly covalent, can readily participate in ionic reactions through polarization. The carbon group bonded to tin acts as a nucleophile and the tin moiety acts as an electrophile.

The great majority of silicon and tin compounds exist as tetracoordinate species, in which silicon or tin occupies the central position in an essentially tetrahedral configuration. They

might therefore be considered as coordinatively saturated octet species. Unlike their carbon analogs, however, the empty d orbitals of the higher members of the Group IVA elements can provide extra coordination sites. Thus organosilicons can act as weak electrophiles. The high polarizability of the Sn-C bond, together with the availability of d orbitals, makes organotins reasonably good electrophiles.

It may be pointed out that the generally low nucleophilicity and electrophilicity of organosilicons make certain silicon-containing moieties good protecting groups (Sect. 6.4.2.4).

Some representative single-bond energy values for bonds to C, Si, and Sn are summarized in Table 6.2.

Table 6.2 Single-Bond Energy Values for Bonds to C, Si, and Sn

	C (6.6) ^a	Si (6.6) ^a	Sn (6.3) ^b
H	99	70 to 76	35
C	83	69 to 76	46 to 60
Si	69 to 76	42 to 53	-
Sn	50 to 60	-	50
N	70	80	65 to 70
O	84 to 86	88 to 108	95
F	105 to 111	129 to 135	-
Cl	79 to 81	86 to 91	85
Br	66 to 68	69 to 74	76
I	58 to 61	51 to 56	62

^a Page 25 of Ref. 6.6

^b These values are for Me_3SnX (p. 9 of Ref. 6.3).

It is noteworthy that the Si-X and Sn-X bonds, where X = H and C, are weaker than the corresponding C-X bonds, whereas the bonds to silicon and tin are stronger than the bonds to carbon when X = N, O, or halogen (except I). Since N, O, and halogens can donate a lone pair of p electrons, these bond energy data can most readily be interpreted in terms of $p_{\pi}-d_{\pi}$ interaction involving the empty d orbitals of silicon and tin.

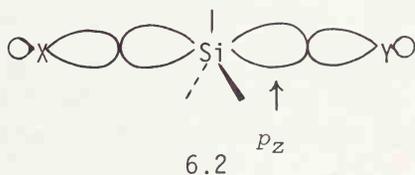
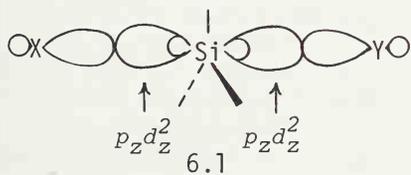
Another important point to be noted is that even the Si-H and Si-C bonds are thermodynamically relatively strong bonds. In fact, the homolytic cleavage of the Si-C bond is generally not a facile process. This property must be at least in part responsible for the development of various thermally stable organosilicon polymers which have found a number of significant practical applications. Although much weaker than the Si-C bond, typical Sn-C bonds do not readily react with a free radical either. On the

other hand, the Si-H and Sn-H bonds are quite reactive toward free-radical species. The difference between the Si-C and Si-H bonds cannot be interpreted in terms of their bond energies. The high reactivity of the bonds to hydrogen relative to the reactivity of the corresponding bonds to carbon is reminiscent of the situation with respect to the relative reactivities of the B-H and B-C bonds (Sect. 5.2.3.6). Although not clear, these differences may qualitatively be attributable to the spherical nature of the s orbital of hydrogen and its sterically least demanding nature, which presumably permit an approach of the attacking species with minimum steric congestion.

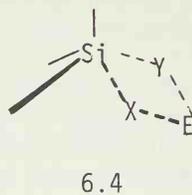
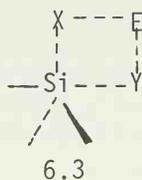
6.1.2 Silicon-Hetero Atom and Tin-Hetero Atom Bonds

As mentioned earlier, the Si-X and Sn-X bonds, where X = N, O, F, Cl, and Br, are thermodynamically quite stable. These bonds, however, are chemically highly labile and readily participate in various substitution reactions. For example, they can be cleaved readily with water or alcohols. This fact is also responsible for the effectiveness of trialkylsilyl groups as hydroxy- and amino-protection groups. The large size of silicon (covalent radius 1.17 Å) compared to that of carbon (covalent radius 0.77 Å), the greater polarizability of the Si-X bond relative to that of the C-X bond, and the possible participation of the silicon $3d$ orbitals appear to be the major factors responsible for the greater ease of substitution reactions at silicon than at carbon.

The mechanistic pathways for substitution reactions taking place at silicon centers have been studied and discussed in detail by Sommer (6.6). In brief, these substitution reactions proceed either with inversion or retention of configuration at the silicon center. The S_N1 mechanism, which would lead to racemization, rarely operates. The inversion reactions most probably proceed by one or more types of S_N2 mechanisms, which may or may not involve an unstable intermediate. On the other hand, formation of a full-fledged pentacovalent silicon intermediate in a rate-determining step appears to be highly unlikely based on the stereochemical and kinetic results. One of the $3d$ orbitals may participate in the inversion reactions, as for example, in 6.1. The results, however, can also be accommodated by the conventional S_N2 mechanism (6.2) involving no $3d$ orbital participation.



The retention reactions most probably involve quasicyclic transition states which are generally four-centered as in 6.3 and 6.4.



6.1.3 Effect of the Silicon or Tin Atom on the Stability of a Cation, Anion, or Free-Radical Center

The stability of a cation, anion, or free-radical center that is close to the silicon or tin atom can be greatly influenced by the metal atom. The availability of the d orbitals and the inductive and conjugative effect of the M-C bond appear to be mainly responsible for the observed influences. The available information allows us to make the following generalizations summarized in Table 6.3.

Table 6.3. Effect of the Silicon or Tin Atom on the Stability of a Cation, Anion, or Free-Radical Center

Type	Metal	Position	
		α	β
Cation	Si	Slightly destabilized (?)	Stabilized (σ - π conjugation)
Cation	Sn	Stabilized (+I effect)	Stabilized (α - π conjugation)
Anion	Si	Somewhat stabilized (p_{π} - d_{π} interaction)	?
Anion	Sn	Somewhat stabilized (p_{π} - d_{π} interaction)	?
Free radical	Si	Stabilized (p_{π} - d_{π} interaction)	?
Free radical	Sn	Stabilized (p_{π} - d_{π} interaction)	Stabilized (σ - π conjugation)

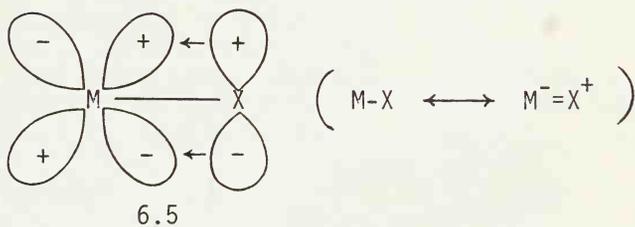
6.2 STRUCTURE

6.2.1 Tetracoordinate Species and Optical Property

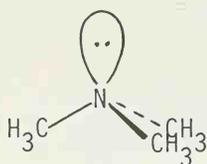
As mentioned earlier, the majority of organometallics containing silicon or tin exist as unassociated tetracoordinate species in which the metal atoms occupy the central position of an essentially tetrahedral configuration. In fact, tetraalkylsilanes and tetraalkylstannanes resemble branched paraffins of similar molecular weights with respect to boiling point, solubility, and appearance. When the four groups bonded to the metal atom are different, the metal atom provides a chiral center. A number of such chiral organosilanes and organostannanes have been prepared and isolated as optically active species, indicating that such chiral centers are stereochemically rigid (6.6).

6.2.1.1 Multiple Bonding Involving Silicon and Tin

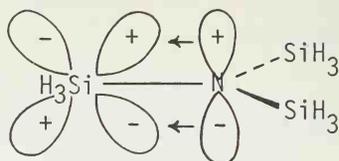
$p_{\pi}-d_{\pi}$ Bond There is little doubt that $p_{\pi}-d_{\pi}$ bonding (6.5) plays an important role in many species containing the Group IVA metals. The bond parameters, such as dissociation energy and bond length, clearly point to the significance of the $p_{\pi}-d_{\pi}$ bonding in the bond between silicon or tin and N, O, or halogens.



Stereochemical data also corroborate the above conclusion. Thus unlike trialkylamines, which are pyramidal, trisilylamines, such as $N(\text{SiH}_3)_3$, are planar. The $p_{\pi}-d_{\pi}$ bonding between nitrogen and silicon must be responsible for planarity. Despite the partial double-bond character, however, the rotation about the Si-X or Sn-X bond, where X = N, O, or halogen, is usually not frozen at ambient temperature.

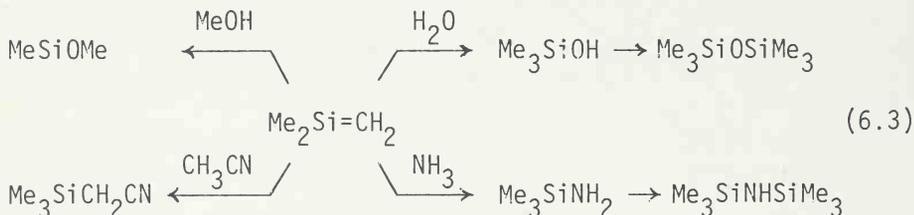
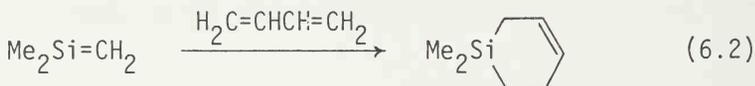
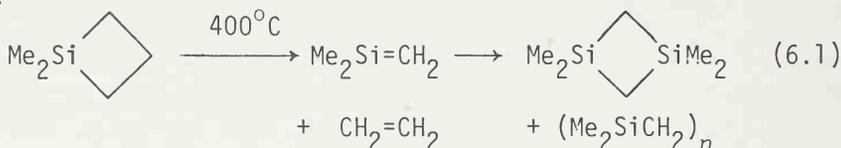


pyramidal

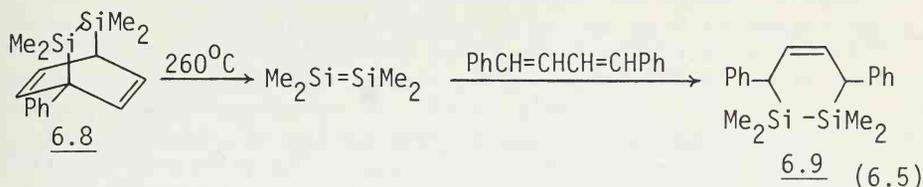
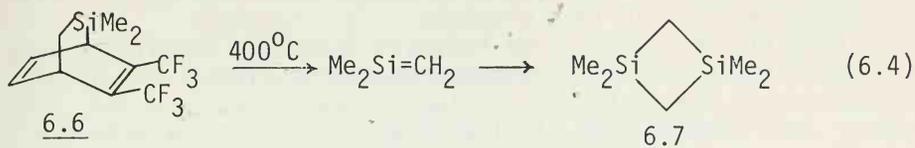


planar

$p_{\pi}-p_{\pi}$ Interaction Despite the great abundance of stable C=C and C≡C compounds, there has been no isolated example of organometallics containing the Si=X or Sn=X bond of the $p_{\pi}-p_{\pi}$ type where X = C, O, N, and so on. The existence of the Si=X species, where X = C, N, O, S, or Si, as short-lived species, however, has been amply demonstrated in recent years (6.7). Thus, for example, the following transformations and trapping experiments are readily interpreted only if one assumes the intermediacy of $\text{Me}_2\text{Si}=\text{CH}_2$ (6.7).



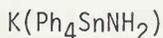
One of the most facile thermal routes to Si=C and Si=Si compounds involves pyrolysis of the corresponding bicyclo[2.2.2]octadienes, for example, 6.6 (6.8) and 6.8 (6.9).



The exact reason for the instability of these species containing Si=X bonds is not clear. Pitzer has postulated that the low π -bond strength is due to the repulsion between bonding orbitals and filled inner shells (6.10). On the other hand, Mulliken (6.11) has proposed that the low π -bond stability might merely mean that the π -bonded products, that is, cyclodimers and polymers, are more stable than the Si=X compounds and that the kinetic barriers to such interconversions are low.

6.2.1.2 Penta- and Hexacoordinate Complexes

The availability of empty d orbitals for coordination suggests the existence of complexes in which the coordination number is greater than four. In addition to various presumed intermediates, which are believed to be pentacoordinate species, a number of penta- and hexacoordinate species containing Group IVA elements, such as 6.10 and 6.11, have been characterized (6.12, 6.13)



6.10



6.11

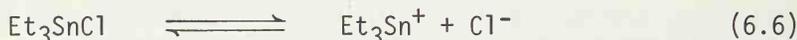
6.2.1.3 Tricoordinate Anions, Cations, and Free Radicals

As described in the following section, a number of bimetallic complexes of the $\text{M}(\text{M}'\text{R}_3)$ type, where M = alkali metal and M' = Si, Ge, Sn, or Pb, have been prepared (6.14). The $\text{M}'\text{R}_3$ moiety may be viewed as a tricoordinate anionic species. Although thermodynamically stable, they are chemically highly active as nucleo-

philes, and have demonstrated some useful synthetic capabilities, as discussed later in this chapter.

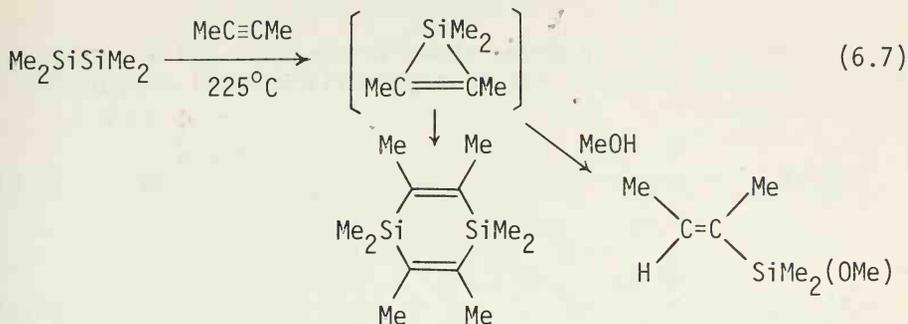
The silicon and tin free radicals have been postulated as intermediates in various reactions of organosilicons and organotins and have been detected spectroscopically (6.15, 6.16). Bond energy data suggest that silyl radicals are poor abstractors of hydrogen from organic molecules, but are good abstractors of halogens.

Highly elusive has been the tricoordinate silicon cation, called either siliconium ion or silelinium ion (6.17). For gaseous silicon atom ($3p^2 3p^2$) the first ionization energy to form silicon anion is 187.9 kcal/mole, whereas the corresponding value for carbon is 259.5 kcal/mole (6.6). In solution, however, solvation plays an important role, thereby making the formation of carbocations a relatively facile process. The formation of sili-cation cations in solution appears to be a highly unfavorable process. On the other hand, certain Sn-X bonds are easily polarizable so that organotins with strongly negative ligands, such as halogens, dissociate to a minor extent. For example, the specific conductance of Et_3SnCl is $1.8 \times 10^{-9} \text{ ohm}^{-1}\text{cm}^{-1}$ at 20°C in benzene. The following dissociation must be responsible for the conductivity.



6.2.1.4 Discoordinate Species

Discoordinate species, MX_2 , containing Si, Ge, Sn, and Pb are analogs of carbenes. Divalent silicon derivatives (silylenes) have been known for many decades and the thermodynamic stability of the divalent state of silicon has been long recognized. Especially noteworthy is the stability of SiF_2 , the half-life of which is about 150 sec at low pressure and ambient temperature (6.18). Although less stable, diorganosilylenes, such as Me_2Si , have also been generated as reactive intermediates. The chemistry of silylenes has been reviewed extensively (6.18, 6.19). Through the use of bulky ligands, for example, $(\text{Me}_3\text{Si})_2\text{CH}^-$, diorganometals containing Ge, Sn, and Pb, which are monomeric in benzene or cyclohexane, have been obtained (6.20). These carbene analogs of the Group IVA metals exhibit chemical behavior similar to that of carbenes. Thus they undergo insertion reactions, as shown in eq. 6.7 (6.19), and formation of complexes with transition metal compounds (6.20, 6.21).



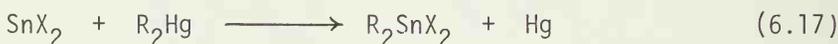
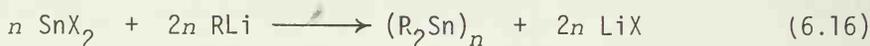
6.3 PREPARATION OF ORGANOSILICONS AND ORGANOTINS

Transmetallation (Method XI) and hydrometallation (Method VI) represent the two most common laboratory methods for the synthesis of organosilicons and organotins, while oxidative metallation (Method I) of organic halides ("direct synthesis") is the most significant industrial method for the synthesis of organosilicons, which is also applicable to the synthesis of certain organotin compounds. The reactions of silyl anions (SiX_3^-) and stannyl anions (SnX_3^-) with organic halides and α,β -unsaturated carbonyl compounds (Method II) appear highly promising as routes to organosilicons and organotins. The great majority of organosilicons and organotins have been prepared by these four general methods. Although much less general, oxidative coupling involving divalent silicon and tin compounds, discussed in the preceding section, provides a unique method of preparation.

6.3.1 Oxidative Metallation with Silicon and Tin

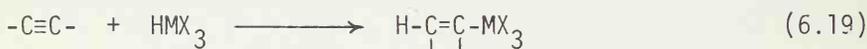
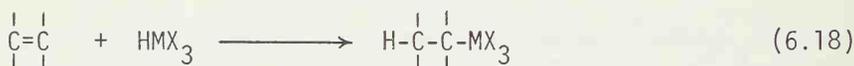
The so-called direct synthesis of organosilicons and organotins consists of the high-temperature reaction (100 to 550°C) of alkyl or aryl halides, usually chlorides or bromides with metallic silicon or tin usually in the presence of a catalyst, such as metallic Cu, Ag, or Zn. This method provides a basis for the preparation in industry of Me_2SiCl_2 , Ph_2SiCl_2 , and other organohalosilanes. Despite its industrial significance, however, the method is not frequently used in research laboratories presumably due to the rather drastic conditions required. Therefore, no detailed discussion of the method is presented here. Interested readers are referred to pertinent monographs (6.1 to 6.5, 6.22) and reviews (6.23).

The reaction of SnX_2 with polar organometallics, such as those containing Li, Mg,² and Zn produces polymeric products, as shown in eq. 6.16, while their reaction with organometallics of heavy metals, such as Hg, Tl, and Pb, involves oxidative-reductive transmetallation (Method XII), as shown in eq. 6.17 (6.1, 6.3 to 6.5).



6.3.3 Hydrosilation and Hydrostannation

The Group IVA metal hydrides react with the C=C and C≡C bonds to form the corresponding addition products as shown in eq. 6.18 and 6.19.



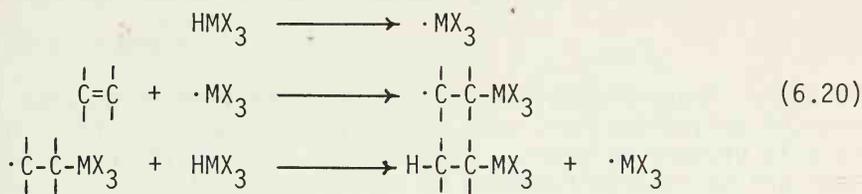
M = Si, Ge, Sn, or Pb

The reaction of hydrosilanes, discovered in 1947 (6.24), is usually called hydrosilylation, whereas both hydrostannation and hydrostannylation have been used for the H-Sn reaction (6.25). If we were to adopt hydrostannylation for the H-Sn reaction, the reaction of boron hydrides, for example, should be called hydroborylation. For the sake of consistency and simplicity, we tentatively adopt the simpler of the two conventions in this book. Thus the M-H addition reactions, where M = Si, Ge, Sn, and Pb, will be termed hydrosilation, hydrogermation (6.26), hydrostannation, and hydroplumbation (6.27), respectively. In addition to several monographs covering all aspects of organosilicon and organotin chemistry (6.1 to 6.5), there is a monograph devoted to the reactions of the Group IVA metal hydrides with the C=C and C≡C bonds (6.28).

6.3.3.1 Free-Radical Hydrosilation

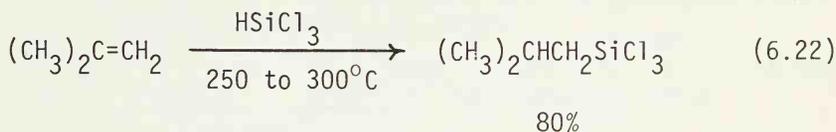
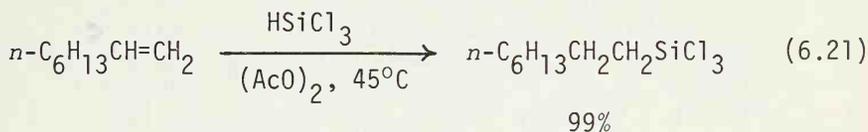
Hydrosilanes add to unsaturated compounds at temperatures of about 300°C without a catalyst. The reaction can be promoted by γ -radiation, UV irradiation, and electric discharges and catalyzed by

various free-radical initiators, such as peroxides and azonitriles. Under these conditions, hydrosilation appears to proceed generally by a free-radical mechanism shown in eq 6.20.

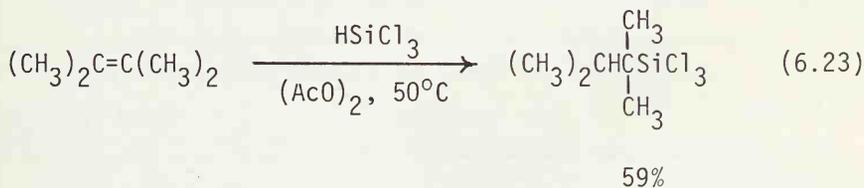


M = Si or Sn

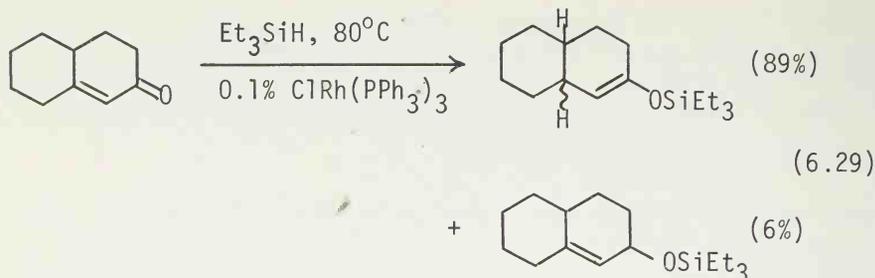
In accordance with the mechanism presented above, the silicon-containing group adds to the C=C or C≡C group such that the more stable of the two possible free radicals is formed either exclusively or predominantly (6.28).



Even highly hindered olefins can be readily hydrosilated with appropriate hydrosilanes (6.28).



There are a few serious limitations. Firstly, the hydrosilation reaction carried out under the free-radical conditions is nonstereoselective (eq. 6.24)



As discussed later (Sect. 10.1), the transition metal-catalyzed hydrosilylation most probably involves a sequence consisting of (1) formation of a transition metal hydride species, (2) its addition to the C=C or C≡C bond, and (3) transmetalation to produce the desired organosilanes.

6.3.3.3 Miscellaneous Hydrosilylation Reactions

The hydrosilylation reaction can also be catalyzed by various other types of compounds, such as tertiary amines (6.28), triorganophosphines, and various metals and their derivatives, such as Na, Zn, ZnCl₂, TiCl₄, and ZrCl₄ (6.28). Some of these catalysts appear capable of inducing Si-H-addition reactions which proceed by totally different mechanisms than those discussed above. For example, the addition of SiHCl₃ to phenylacetylene in the presence of a tertiary amine evidently involves a nucleophilic addition of ⁻SiCl₃ generated by the reaction of SiHCl₃ with the added tertiary amine (6.32). At present it is not clear, however, if any of these less-known procedures will provide any unique advantages over the ones discussed earlier.

6.3.3.4 Hydrostannation

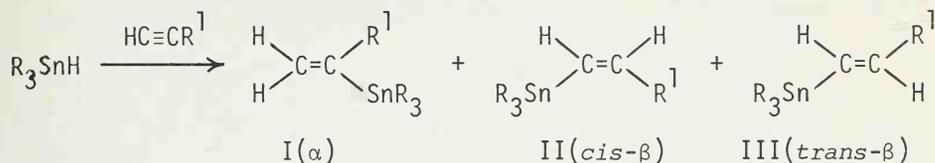
The hydrostannation reaction takes place considerably more readily than the corresponding hydrosilylation reaction, and is usually carried out at 80 to 100°C either in the absence of a catalyst or in the presence of catalytic amounts of free-radical initiators. The applicability of various catalysts, such as those used in the hydrosilylation reaction, does not appear to have been well delineated.

Both olefins and acetylenes can readily be hydrostannated. The reaction of acetylenes with trialkylstannanes producing the corresponding alkenyltrialkylstannanes, however, is of particular synthetic interest, since the alkenyl group of such products can be selectively transferred from tin to various other atoms including C, H, halogen, and Li while retaining the structural inte-

grity of the alkenyl group.

The regio- and stereochemistry of the triorganostannane-acetylene reaction has been investigated extensively, and some representative results are summarized in Table 6.5 (6.33 to 6.36).

Table 6.5 The Reaction of Triorganostannanes with Acetylenes

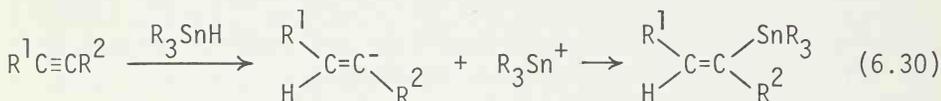


R	R ¹	Reaction Cond.		Yield (%)				Ref.
		Temp.	Time	Total	I	II	III	
Me	Bu	60°C,	7 hr	85	2	29	69	6.33
Ph	Bu	50°C,	3 hr	>80	0	85	15	6.33
Et	Ph	60°C,	7 hr	75	0	70	30	6.33
Ph	Ph	60°C,	1 hr	90	0	28	72	6.33
Bu	$\begin{array}{c} H \\ \\ CH_2COTHP \\ \\ CH_3 \end{array}$	95°C,	-	92	-	15	85	6.34
Bu	CH ₂ OTHP	80°C,	2 hr	89	0	0	100	6.35
Et	CH ₂ OH	100°C,	6 hr	>70	25	45	30	6.33
Pr	COOMe	55°C,	6 hr	72	31	36	33	6.33
Et	CN	20°C,	1 hr	100	100	0	0	6.33
Et	OEt	50°C,	1.5 hr	100	4	91	5	6.33
Bu	SnBu ₃	-	-	88	0	0	100	6.36

Before attempting to interpret these results, a word of caution may be in order. It has been found that, under the hydrostannation conditions, the hydrostannated products can undergo

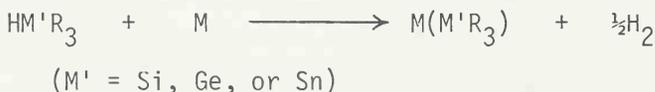
isomerization. Therefore, the observed product distribution does not usually represent that of the initial kinetic products. Despite such a complication, the following tentative generalization can be made. Firstly, an electron-donating substituent (R^1) places the tin atom predominantly or exclusively on the β -carbon atom, while an electron-withdrawing substituent directs the tin atom more to the α -carbon atom. Secondly, hydrostannation is generally not highly stereoselective. It appears that, under kinetic conditions, trans addition predominates, whereas the trans isomers (i.e., cis addition products) tend to predominate under thermodynamic conditions.

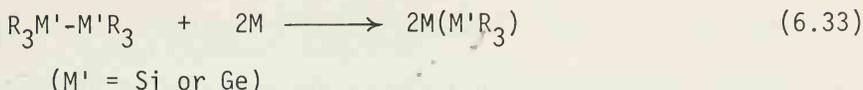
The mechanism of hydrostannation does not appear to have been well-established. In some cases, the reaction is facilitated by the addition of free-radical initiators, such as azobisisobutyronitrile (AIBN), suggesting that the reaction proceeds at least partially by a free-radical mechanism (6.28). On the other hand, examination of the effects of substituents, solvents, and isotopes and of the kinetics suggests that the reaction involves a stepwise trans addition of a hydride and a triorgano-stannyl cation (R_3Sn^+) (6.33). It is clear that further investigation is needed to clarify the mechanistic details.



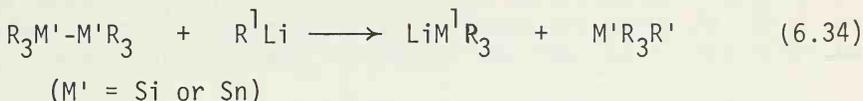
6.3.4 Organosilicons and Organotins via Silyl and Stannyl Anions

Various methods for preparing organometallics with metal-alkali metal bonds have been reviewed in detail (6.14). There are several routes to bimetallic compounds of the $M(M'R_3)$ type, where M = alkali metal, and M' = Si, Ge, Sn, or Pb (eqs. 6.31 to 6.33).

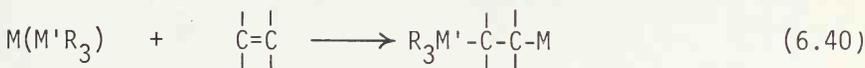
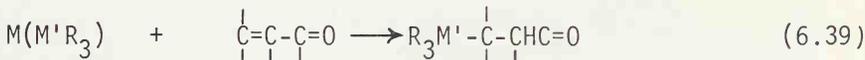
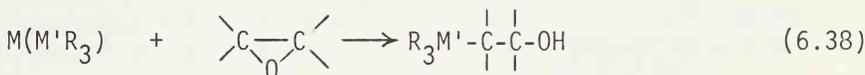
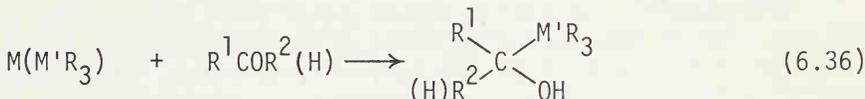
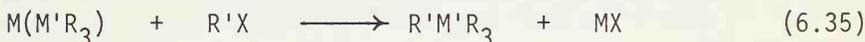




These three methods require an alkali metal as a reagent. More recently, the following convenient method involving the use of organolithiums has been developed (6.37, 6.38).



In many respects triorganosilylmetals ($MSiR_3$) and triorganostannylmetals ($M SnR_3$), where M = alkali metals, behave just like organoalkali metals (6.14). They are strong bases as well as excellent nucleophiles. Only those reactions that involve the Si-C or Sn-C bond formation are discussed here. The general patterns of their reactions with typical carbon electrophiles are summarized in eqs. 6.35 to 6.40.



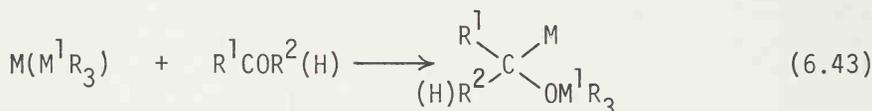
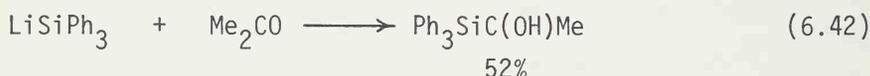
All of these reactions provide routes to organosilicons and organotins.

The reaction with organic halides is often complicated by the alkali metal-halogen exchange reaction (6.14).



At present, the synthetic utility of the reaction of $M(M^1R_3)$ with organic halides is not clear, since the same products usually can be obtained in a more satisfactory manner by the reaction of XM^1R_3 with MR^1 .

The reaction with aldehydes and ketones provides a convenient route to α -hydroxysilanes and α -hydroxystannanes, for example, eq. 6.42, although the reaction is often complicated by abnormal addition (eq. 6.43) and enolization of the carbonyl compounds.



Due to various competing side reactions, the reaction with acyl halides is generally poor as a route to acylsilanes and acylstannanes (6.14).

Both acyclic and cyclic ethers react with $MSiR_3$ and $MsnR_3$. The reaction of epoxides with these organometallics is facile, producing β -hydroxysilanes and β -hydroxystannanes. The reaction generally involves a highly stereospecific trans attack of the least hindered carbon atom. Thus the reaction presumably occurs by an S_N2 mechanism. As detailed later, β -heterosubstituted organosilicons and organostannanes readily undergo β -elimination. Thus epoxides can be readily deoxygenated by the following sequence, which involves an overall inversion of configuration. Since olefins can be converted to epoxides with retention of configuration, the epoxidation-silylation-elimination sequence (eq. 6.44) achieves inversion of configuration of olefins (6.39).

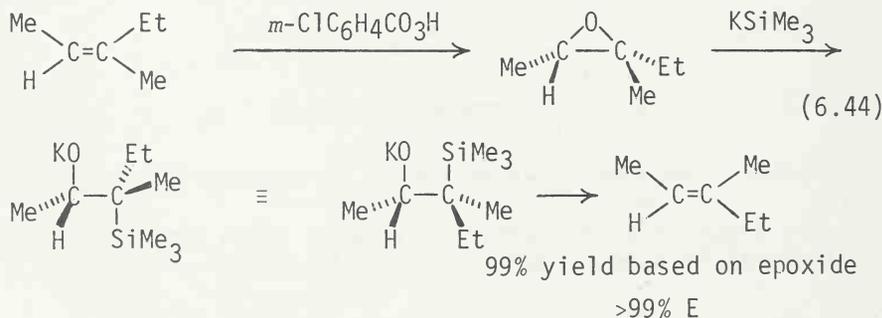
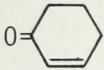
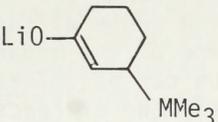
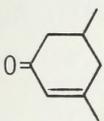
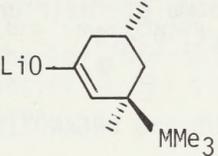
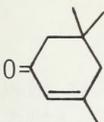
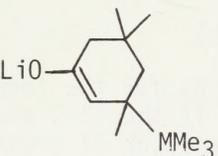
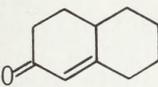
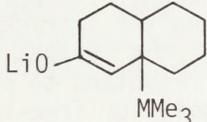
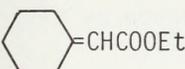
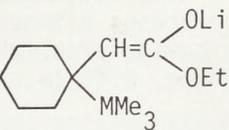
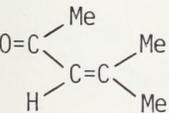
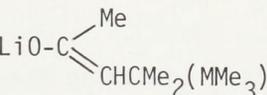


Table 6.6 The Reaction of LiSiMe_3 and LiSnMe_3 with α,β -Unsaturated Carbonyl Compounds

α,β -Unsaturated Carbonyl Compound	Product	Yield (%)	
		M = Si	M = Sn
		97	96
		78	93
		0	77
		-	94
		-	80
		-	93

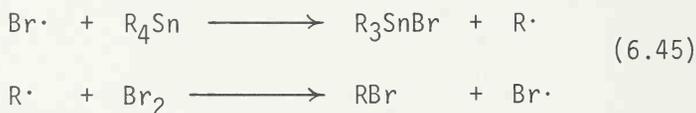
The bimetallic compounds of the MSiR_3 or MSnR_3 type react with various olefins and acetylenes to give the corresponding addition products. The results observed with unactivated olefins and acetylenes, such as ethylene, are not encouraging. The addition reaction, however, proceeds nicely with certain activated olefins and acetylenes, especially with α,β -unsaturated carbonyl compounds, to give the corresponding 1,4-addition products. The scope and limitation of the reaction of LiSiMe_3 (6.37) and (6.38) with α,β -unsaturated carbonyl compounds are indicated in Table 6.6. It should be noted that the scope of the conjugate addition reaction with LiSnMe_3 is one of the broadest in that high steric hindrance at the β -carbon can be tolerated. The axial attack appears to be the preferred mode of reaction. The products behave as typical lithium enolates in their protonation, silylation, and alkylation (6.14). Some of their unique synthetic applications are discussed in Sect. 6.4.3.

6.4 REACTIONS OF ORGANOSILICONS AND ORGANOTINS

6.4.1 General Reaction Patterns

In the preceding section, methods for the formation of the Si-C and Sn-C bonds are discussed. If the Si-C and Sn-C bonds were to directly participate in the formation of organic compounds that do not contain silicon or tin, these bonds would somehow have to be cleaved.

The discussion presented in Sect. 6.1. permits the following tentative generalization concerning the intrinsic reactivity of the Si-C and Sn-C bonds. Firstly, the typical unactivated Si-C bond, such as the Si-Et bond, is reluctant to participate directly in either nucleophile-electrophile or free-radical reactions. Secondly, the Sn-C bond is considerably more reactive toward both electrophiles and nucleophiles. Thirdly, homolytic cleavage of the Sn-C bond is not a facile process, although certain reactions of organotins involving Sn-C cleavage presumably proceed by free-radical mechanisms, as shown in eq. 6.45 (6.40, 6.41).

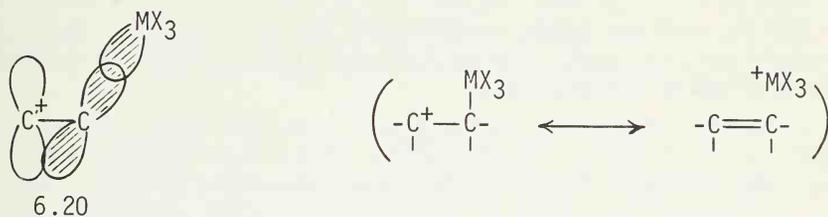


6.4.1.1 Free-Radical Reactions Involving the Cleavage of the Si-C or Sn-C Bond

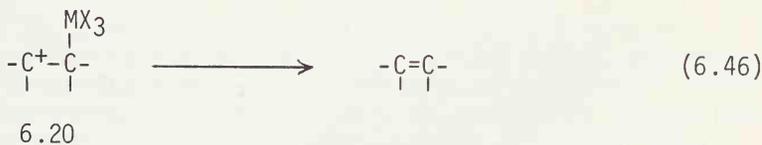
Based on the generalization presented above, it is not surprising that there are very few synthetically useful reactions involving homolytic cleavage of the Si-C or Sn-C bond.

6.4.1.2 Reaction with Electrophiles -- Significance of σ - π Conjugation

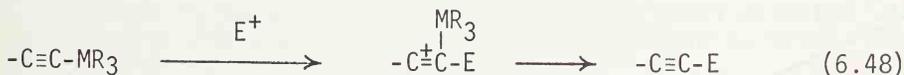
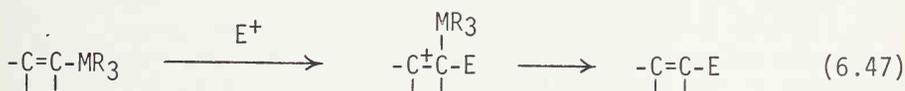
Certain functionalized organometallics of the Group IVA elements are highly reactive toward a variety of electrophiles. Those organometallics that readily participate in reactions with electrophiles include (1) α,β -unsaturated derivatives, such as alkenyl, aryl, and alkynyl derivatives, and (2) β,γ -unsaturated derivatives, such as allyl and benzyl derivatives. Mechanistic studies by Eaborn (6.42) and Traylor (6.43) have revealed that these reactions proceed stepwise without involving direct M-C bond cleavage, and that the key intermediate is the β -silyl or β -stannyl carbocationic species (6.20) stabilized through σ - π conjugation (hyperconjugation).

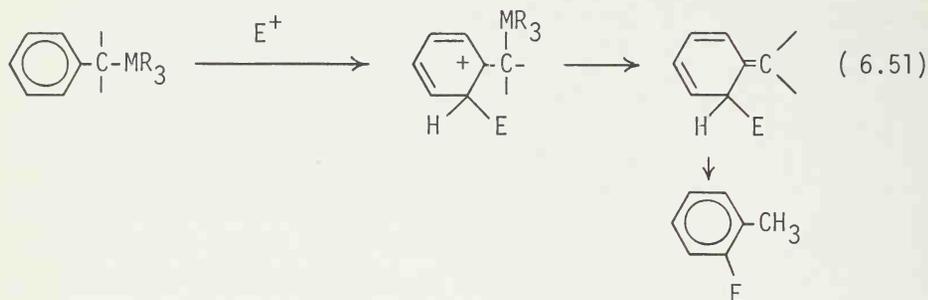
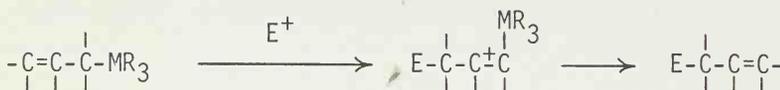
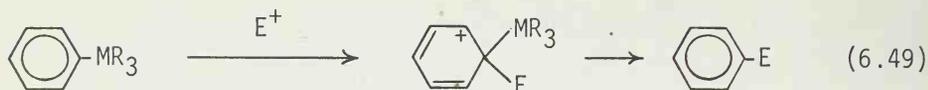


Quite significantly, the β -silyl or β -stannyl carbocation 6.20 undergoes a spontaneous elimination reaction to form the corresponding unsaturated organic compounds (eq. 6.46).

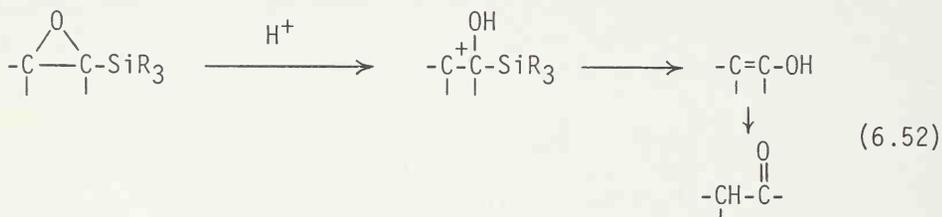


Several representative reaction schemes involving the intermediacy of 6.20 are shown in eqs. 6.47 to 6.51.





There can be various other routes to 6.20, for example, eq. 6.52. It appears that in each case we can expect to obtain the corresponding elimination product.



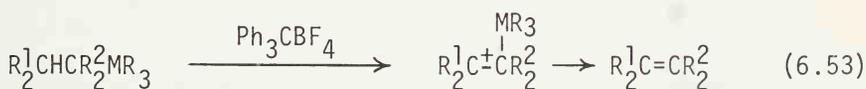
The significance of σ - π conjugation and of 6.20 as a key intermediate in the reactions of organometallics containing the Group IVA elements must be stressed. The magnitude of the σ - π conjugation effect may be appreciated by comparing the electron-donating ability of silicon- and tin-containing groups with that of more familiar organic groups, such as Me and MeO groups (6.43c). As shown in Table 6.7, the electron-donating ability of the CH_2SnPh_3 and CH_2SnMe_3 groups, which has been shown to be largely due to σ - π conjugation rather than inductive effects, is either comparable to or greater than that of the MeO group. Other factors being comparable, the magnitude of the conjugation effect increases in the order: $\text{Si} < \text{Ge} \ll \text{Sn} \ll \text{Pb}$. Thus, for example, the relative rates of cleavage of PhMeT_3 by aqueous methanolic perchloric acids are: Si, 1; Ge, 36; Sn, 3.5×10^5 ; and Pb,

2×10^8 (6.44). The relative reactivity appears to be a function of (1) M-C bond energy, (2) polarizability, and (3) steric hindrance. The scope of the reactions proceeding via 6.20 is discussed further later in this chapter.

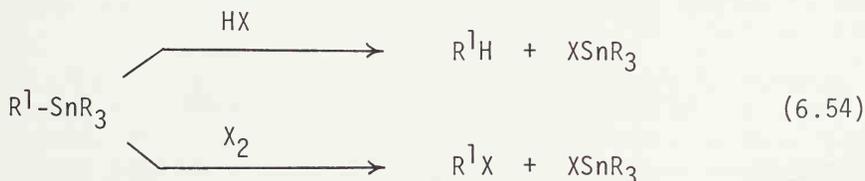
Talbe 6.7 Substituent Constants (σ^+)

Substituent	σ^+ Constant
-Me	-0.30
-OMe	-0.78
-CH ₂ SiMe ₃	-0.62
-CH ₂ SnMe ₃	-0.92
-CH ₂ SnPh ₃	-0.75
-CH ₂ PbPh ₃	-1.00
-CH ₂ HgPh	-1.20

As mentioned earlier, unactivated Si-C bonds are unreactive toward electrophiles. With certain highly reactive electrophiles, however, even organosilicons containing such unactivated Si-C bonds can participate in reactions in which σ - π conjugation presumably plays a key role (6.45).



The Sn-C bond is considerably more susceptible to attack by electrophiles. Water and aliphatic alcohols are generally inert, but phenols, mercaptans, and carboxylic acids readily cleave the Sn-C bond. The reaction with halogens, such as Br₂ and Cl₂, is also a facile process. Hydrogenolysis with hydrogen is generally difficult.

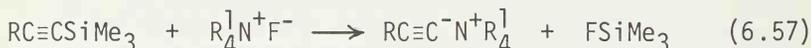


6.4.1.3 Reaction with Nucleophiles

The reaction of the Si-C or Sn-C bond with nucleophiles (Y^-) by direct displacement is another general scheme involving the cleavage of the Si-C or Sn-C bond (eq. 6.55).



The reaction is considerably more facile with organotins than with the corresponding organosilicons. The greater reactivity of organotins relative to that of organosilicons must be due to the higher polarizability and the greater length of the Sn-C bond. The reaction can take place, if (1) the R group is less basic than the Y group, shown in eq. 6.56, (6.46), or (2) the M-Y bond is thermodynamically highly stable and the equilibrium can be shifted by some means, as shown in eq. 6.57, (6.47).



These reactions presumably proceed via the penta-coordinate transition states 6.1 to 6.4 discussed in Sect. 6.1.

6.4.1.4 Intramolecular Interaction of the Si-C and Sn-C Bonds with Nucleophiles and Electrophiles -- Elimination and Rearrangements

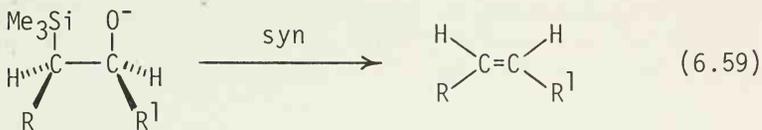
The reaction of the Si-C and Sn-C bonds with polar reagents can also take place intramolecularly. In fact, the intramolecular version of the reaction is often far more facile than the intermolecular counterparts. Such intramolecular reactions usually involve either an elimination or a rearrangement.

By far the most significant reaction from the viewpoint of organic synthesis is the β -elimination reaction of β -heterosubstituted organosilanes and organostannanes (eq. 6.58), which is the E2 version of the β -elimination reaction discussed earlier in this section.

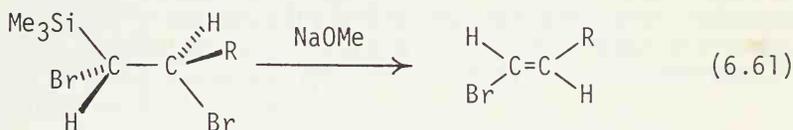


The reaction involves either syn or anti elimination. As a rule

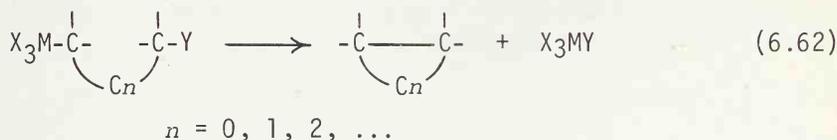
of thumb, syn elimination occurs if (1) the reaction is thermal and spontaneous, that is, unassisted (eq. 6.59), or (2) a highly nucleophilic center is generated at the substituent Y by the action of an added nucleophile (eq. 6.60).



On the other hand, anti elimination takes place, if (1) an added electrophile can activate the Y group (eq. 6.60b), or (2) an added nucleophile can interact with the silicon or tin more readily than with the Y group (eq. 6.61).

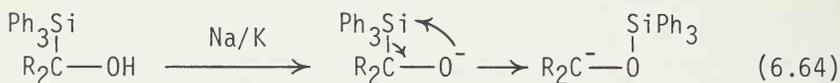
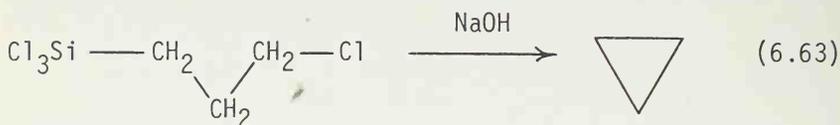


The role of the β -elimination reaction as a key step in various synthetically useful reactions of organosilicons and organotins is discussed further later. It is important to recognize that β -elimination is but one of a series of intramolecular substitution reactions represented by the following general equation (6.62).



In fact, the γ -elimination reaction of γ -halosilanes to form cyclopropanes is also a facile process; see eq. 6.63 (6.48). When an organosilane contains a nucleophilic group bonded to an α -carbon atom, attack of the silicon atom by the nucleophilic moiety

induces a 1,2-migration of the silicon-containing group that migrates as a cationic species (cationotropic rearrangement), see eq. 6.64 (6.49).



This cationotropic rearrangement is closely related to the Wittig rearrangement and the Stevens rearrangement. However, its synthetic usefulness is not clear at present.

6.4.1.5 Miscellaneous Reactions Involving Cleavage of the Si-C or Sn-C Bond

Although the great majority of Si-C or Sn-C cleavage reactions are represented by those discussed above, there are various other modes of cleaving the Si-C or Sn-C bond, of which the following are worth mentioning here: (1) the reaction of the allylic and β -carbonyl derivatives of organosilicons and organotin with organic electrophiles (Sect. 6.4.2.1), (2) oxidation of the Sn-C bond with $\text{CrO}_3 \cdot 2\text{Py}$ to form the corresponding alcohol or ketone (Sect. 6.4.3.1), and (3) the anionotropic 1,2-rearrangement of the silicon-containing group (Sect. 6.4.2.1).

6.4.2 Reactions of Organosilicons

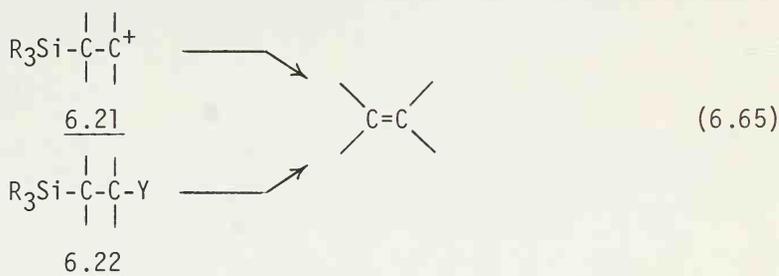
The use of organosilicons in organic synthesis may be classified as follows: (1) the reactions involving cleavage of the Si-C bond, (2) the reactions of the Si-O derivatives, and (3) the reactions of the Si-H bond. As in previous chapters, those reactions that do not involve either cleavage of the Si-C bond or formation of the C-C bond are discussed only briefly.

6.4.2.1 Synthetic Reactions Involving Cleavage of the Si-C bond

As discussed earlier, the intrinsic reactivity of the Si-C bond toward either polar or free-radical reagents is generally low. Thus nonfunctionalized organosilanes rarely participate in the Si-C cleavage reactions. If a functional group is present in an appropriate position, however, usually α , β , and/or γ to the silicon atom, an added reagent may interact with the functional

group. The silicon atom may or may not exert significant influence in this step. In many cases, the product is a silicon-containing compound.

In many other cases, however, the product or intermediate formed in such a reaction can undergo either a thermal or a reagent-assisted reaction involving cleavage of the Si-C bond. As discussed in the preceding section, such intermediate species are represented by either 6.21 or 6.22 in a large number of reactions.

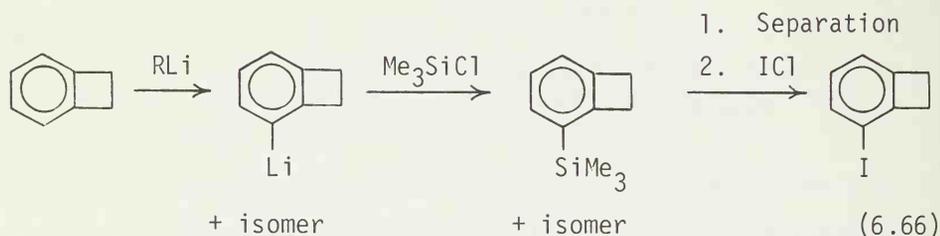


Electrophilic Substitution Reactions The intermediate 6.21 is generally formed by adding an electrophilic species (E^+) to either α,β - or β,γ -unsaturated species. Such reactions are accelerated by the σ - π conjugation effect and are usually highly regioselective (6.42). It is important to note that organostannanes also participate in the same reaction, and that the tin reaction is more facile than the silicon reaction. Some representative electrophiles (E -Y) and their reaction products are summarized in Table 6.8.

Table 6.8 Reaction of Unsaturated Organosilanes ($R^1SiR_2^2$) and Organostannanes ($R^1SnR_2^2$) with Electrophiles

Electrophile	Product	Electrophile	Product
$RCOX + AlCl_3$	R^1COR	$HNO_3 + Ac_2O$	R^1NO_2
$(RCO)_2O + AlCl_3$	R^1COR	$NOCl$	R^1NO
 - $CH_2Br + AlCl_3$	R^1CH_2 - 	$RSO_2X + AlCl_3$	R^1SO_2R
$HX (HCl, HOAc)$	R^1H	SO_3	R^1SO_3H
Br_2	R^1Br	$Hg(OAc)_2$	H^1HgOAc
ICl	R^1I	BCl_3	R^1BCl_2

The reaction offers various advantages over the corresponding reaction of the parent nonmetallated species or of polar organometallics, such as those containing lithium or magnesium. The following specific advantages may be cited for the reactions of arylsilanes: (1) formation of a single regioisomer (ipso isomer), (2) formation of isomers that cannot be obtained by the direct aromatic substitution reaction of the parent compounds, and (3) successful utilization of deactivated aromatics. The following otherwise difficult-to-obtain aromatic iodide can now be prepared by this reaction; see eq. 6.66 (6.50).

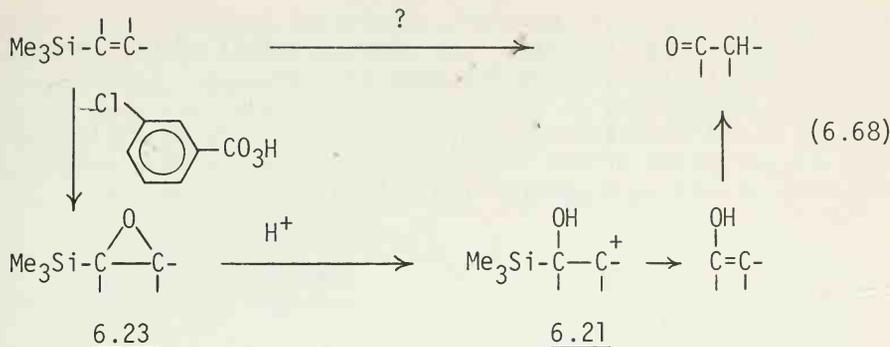


The reaction of alkenylsilanes with electrophiles are not only regioselective but frequently highly stereospecific. In cases where the elimination step does not require addition of a reagent, the overall process proceeds with retention, whereas either retention or inversion may result if the elimination step is assisted by an added reagent (6.51).

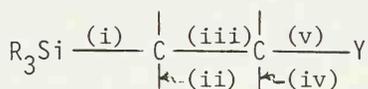


It should be pointed out here that the cationic intermediate 6.21 can also be derived from various organosilicon compounds other than the α,β - and β,γ -unsaturated derivatives. For example, the epoxysilanes 6.23, readily obtainable by epoxidation of alkenylsilanes, can be converted readily to the corresponding ketones. The latter conversion presumably proceeds via 6.21; see eq. 6.68 (6.52). The overall sequence provides a convenient method for the conversion of alkenylsilanes into the corresponding carbonyl compounds.

β -Heterosubstituted Organosilanes as Intermediates It has become increasingly clear in recent years that a number of organosilicon reactions involve the intermediacy of β -heterosubstituted organo-



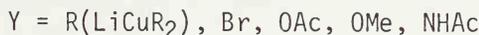
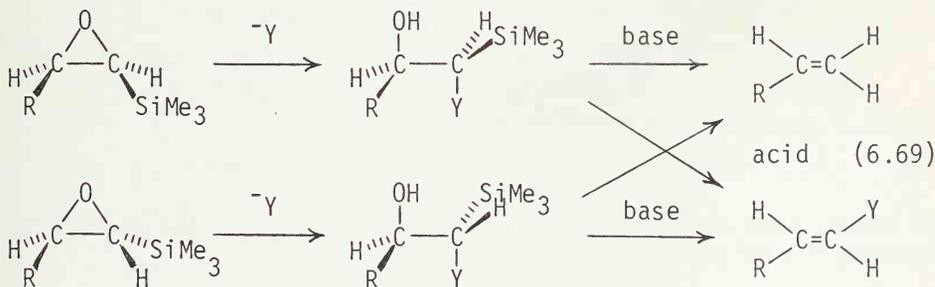
silanes (6.22), which can be converted to the corresponding olefins as discussed earlier. Inspection of 6.22 suggests that it can be generated by forming one or more of the five bonds (i) to (v).



6.22

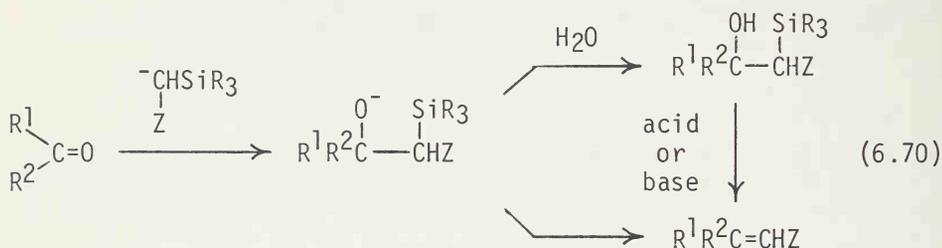
(a) Via formation of bond (i) The reaction of triorganosilyl anions with epoxides produces β -silylalkoxy anions which undergo a facile syn elimination. This sequence can be applied to configurational inversion of olefins, as shown in eq. 6.44 (Sect. 6.3.4).

(b) Via formation of bond (ii) The reaction of epoxysilanes with appropriate nucleophiles produces β -hydroxylilanes; see eq. 6.69 (6.53).



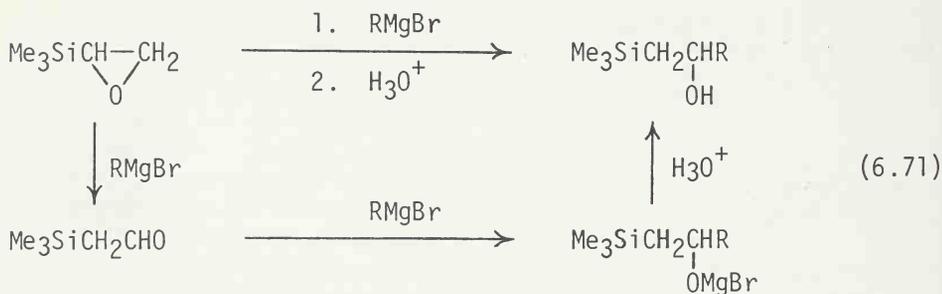
Whereas LiCuR_2 are satisfactory alkylating agents in this reaction, LiR and RMgX are not. The stereochemical results are in accord with the generalization made earlier.

(c) Via formation of bond (iii) A variety of silicon-stabilized carbanion of the ^-CH(Z)SiR_3 type react with aldehydes and ketones, providing a general route to 6.22 (6.54, 6.51).



This reaction provides an alternative to the Wittig olefination reaction. Unfortunately, mixtures of *cis* and *trans* isomers are usually obtained. A wide variety of functional groups have been used as the Z group. They include: COOR , COOH , CN , SiMe_3 , PPh_2 , PO(OEt)_2 , SR , and SOR (6.51). It is interesting to note that the ability of a trialkylsilyl group to interact with a β -oxy anion appears greater than that of the PO(OEt)_2 group.

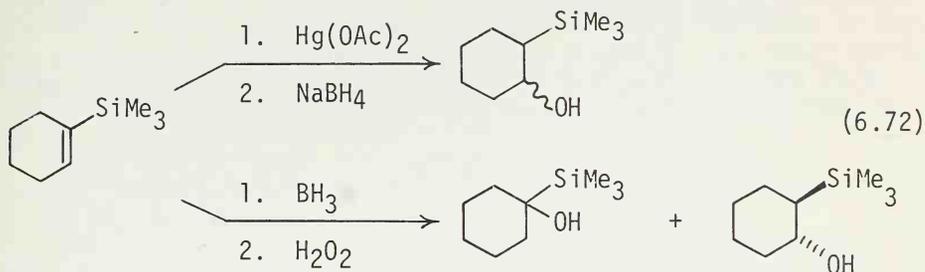
(d) Via formation of bond (iv) Unlike the reaction of trimethylsilylethylene oxide with LiCuR_2 , which involves an α attack by LiCuR_2 , the corresponding reaction of RMgBr takes an anomalous course, as shown in eq. 6.71.



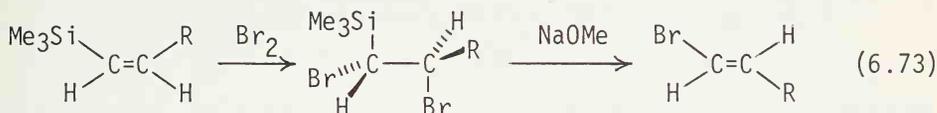
Although such a reaction provides a route to 6.22, its scope and synthetic utility are not clear.

(e) Via formation of bond (v) Hydroboration-oxidation of

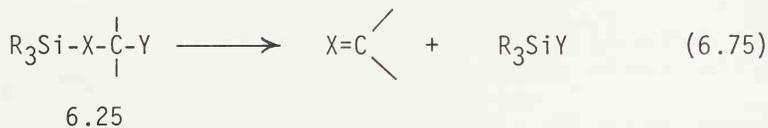
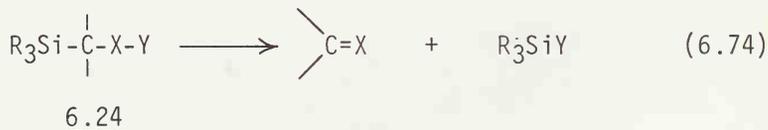
alkenylsilanes produces mixtures of α - and β -hydroxysilanes, as shown in eq. 6.72. As expected, the β -isomers are trans. On the other hand, oxymercuration-demercuration of alkenylsilanes produces only β -isomers, but the reaction is not stereoselective; see eq. 6.72 (6.55).



(f) Via formation of bonds (ii) and (v) Although we have tentatively interpreted the reactions of alkenylsilanes with electrophiles in terms of the intermediacy of 6.20, some of these reactions may form 6.22 as intermediates, as shown in the following example; see eq. 6.73 (6.56).



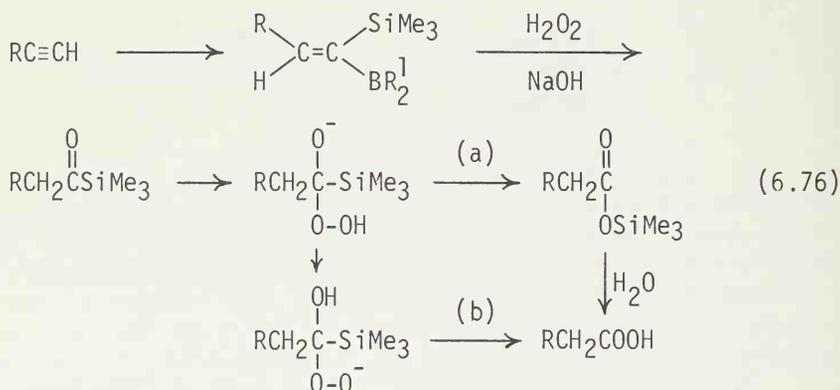
(g) Other β -heterosubstituted organosilanes All of the β -heterosubstituted organosilanes discussed above are represented by 6.22. It may be anticipated, however, that there can be other types of β -heterosubstituted organosilanes represented by 6.24 and 6.25 which would also readily undergo β -elimination.



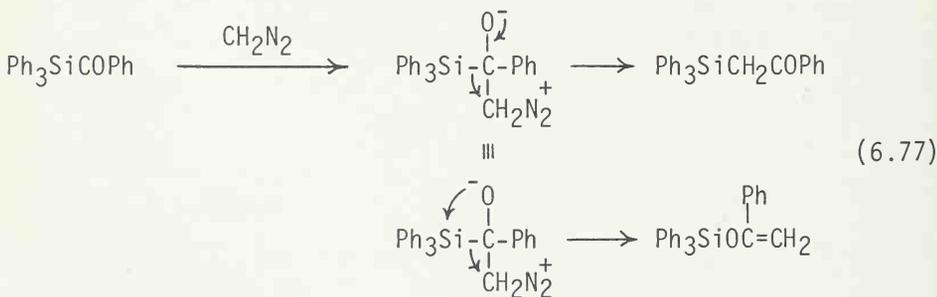
Indeed, as discussed in the following sections, the great majority of the reactions of silyl enol ethers that produce

organic products can be interpreted in terms of eq. 6.75. On the other hand, there have been relatively few reactions that can be represented by eq. 6.74.

The following oxidation reaction (eq. 6.76) which provides a convenient method for the conversion of terminal acetylenes to carboxylic acids has been reported recently (6.57) and interpreted in terms of an anionotropic 1,2-migration of a trialkylsilyl group (path a). Although the proposed mechanism is plausible, it appears equally plausible to interpret the results in terms of the β -elimination reaction of 6.24 (path b).



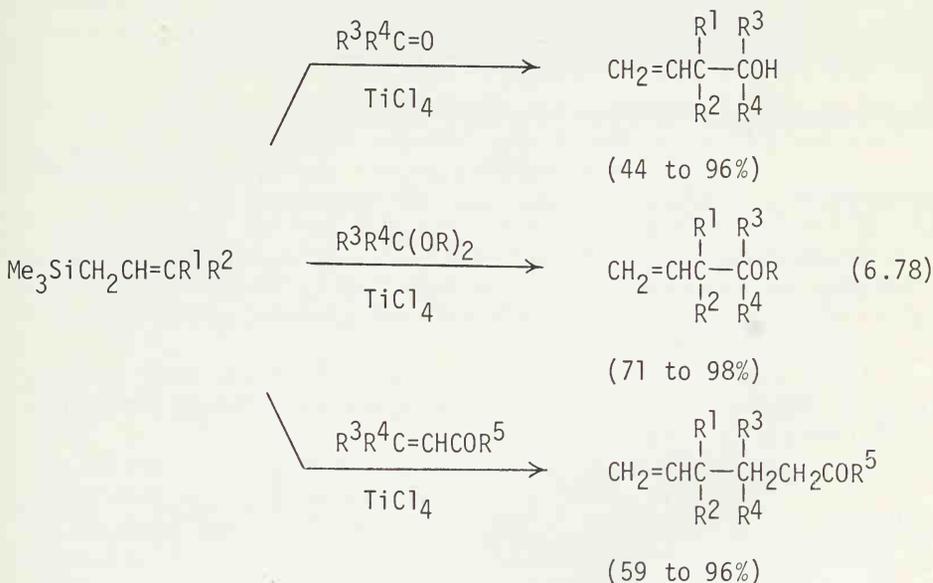
Anionotropic Rearrangements The possibility that the organosilyl group might undergo anionotropic 1,2-migration in addition to cationotropic 1,2-rearrangement (Sect. 6.4.1) is mentioned above. Indeed, studies by Brook and others have revealed that the organosilyl group generally has a considerably greater aptitude than a typical carbon group, such as phenyl, to migrate as an anionic moiety (6.49c), as indicated by the following example (eq. 6.77).



No competitive phenyl migration takes place. It is of interest to note that the presumed intermediate 6.26 evidently undergoes both anionotropic and cationotropic rearrangements competitively. Although very interesting from the mechanistic viewpoint, the synthetic usefulness of such anionotropic rearrangements has not yet been well delineated. The key question here is how to generate the required intermediates in a more practical manner.

Addition Reactions of Allylsilanes Although allylsilanes do not readily react with carbonyl compounds, such as aldehydes and ketones, these reactions can be markedly accelerated by the action of TiCl_4 . The markedly rate-enhancing ability of TiCl_4 was originally investigated in the related reactions of silyl enol ethers, as discussed later (Sect. 6.4.2.2).

The scope of the titanium-promoted allylsilane reactions, being investigated mainly by Sakurai (6.58), has not yet been well delineated. Even so, the following useful procedures have been developed.



These reactions proceed with a complete allylic rearrangement. The conjugate addition reaction appears to be highly general with respect to the structural type of enones.

The mechanism of the reaction is not clear. It may be, however, that these reactions merely represent additional examples of the reaction of allylsilanes with electrophiles in which σ - π conjugation plays a dominant role. If so, the α,β -unsaturated

organosilanes should also react in a similar manner, although this point does not appear to have been clearly established.

6.4.2.2 Reactions of Trialkylsilyl Enol Ethers

The chemistry of silyl enol ethers has been extensively reviewed recently (6.51, 6.59). When enolate anions are treated with trialkylhalosilanes, such as Me_3SiCl , the corresponding trialkylsilyl enol ethers are formed in a highly regiospecific manner and generally in excellent yields. Since the bond energies for the Si-C and Si-O bonds are approximately 70 and 90 kcal/mole, respectively, the oxygen-silylated products are formed exclusively (eq. 6.79).

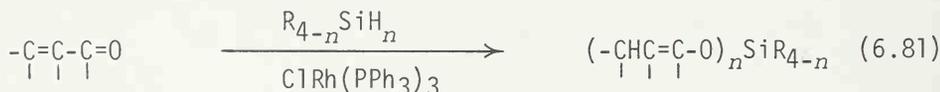


It is feasible, however, to obtain carbon-silylated derivatives by treating α -carbonylorganomercuries with trialkylhalosilanes (6.60). The products are, however, thermally unstable and readily isomerize to form the oxygen-silylated derivatives.

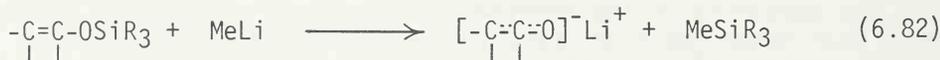


Alternatively, silyl enol ethers can be prepared by treating aldehydes and ketones with either $\text{R}_3\text{SiCl-NEt}_3$ in DMF (6.61) or $\text{R}_3\text{SiCl-NEt}_3\text{-ZnCl}_2$ (6.62). The more stable regioisomers are formed predominantly by this method.

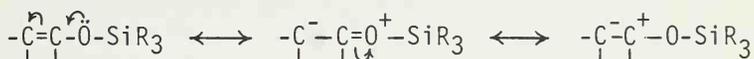
There also exist various other routes to silyl enol ethers, of which the hydrosilation of α,β -unsaturated carbonyl compounds is of reasonable generality (6.63).



Silyl enol ethers can be treated with a variety of strong bases, such as MeLi , to form the corresponding enolate anions in a highly regiospecific manner (eq. 6.82).



Both Si-C and Si-O bonds of trialkylsilyl enol ethers share essentially the same chemical properties as those of other trialkylsilyl ethers discussed in the preceding section. Thus although the Si-O bond can be cleaved easily by hydrolysis and other methods, it is inert to many other reagents. It is soon noted that neither Si-O nor Si-C bond is directly involved in the initial stages of most of the reactions of trialkylsilyl enol ethers. The Si-O bond, however, exerts a strong influence on the chemical properties of the conjugated double and triple bonds mainly through the resonance effect.

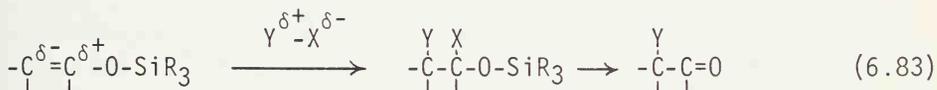


Due to the electron-donating +R effect of the trialkylsilyloxy group, the C=C bond is more nucleophilic than the more usual C=C bond, but it is less nucleophilic than the more ionic enolates, such as lithium enolates. In other words, the general order of reactivities toward electrophiles is:



It may thus be said that trialkylsilyl enol ethers act as (1) trialkylsilyl-moderated enolate anions and (2) activated and functionalized olefins toward electrophiles.

Reactions with Various Halides Various electrophilic halides including halogens, such as Cl₂ and Br₂, have reacted with trialkylsilyl enol ethers according to the following general equation consisting of an addition-elimination sequence (eq. 6.83).



The halide reagents that have been successfully used and the products obtained are summarized in Table 6.9.

Halogenation of silyl enol ethers produces α -halocarbonyl compounds in good yields. It allows regiospecific halogenation of ketones and provides a highly satisfactory method for preparing α -haloaldehydes; see eq. 6.84 (6.64, 6.65d), which are otherwise difficult to obtain.

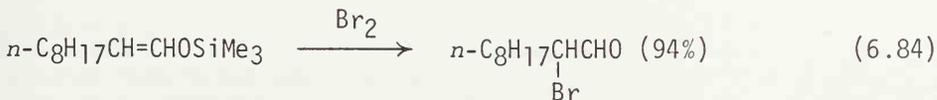
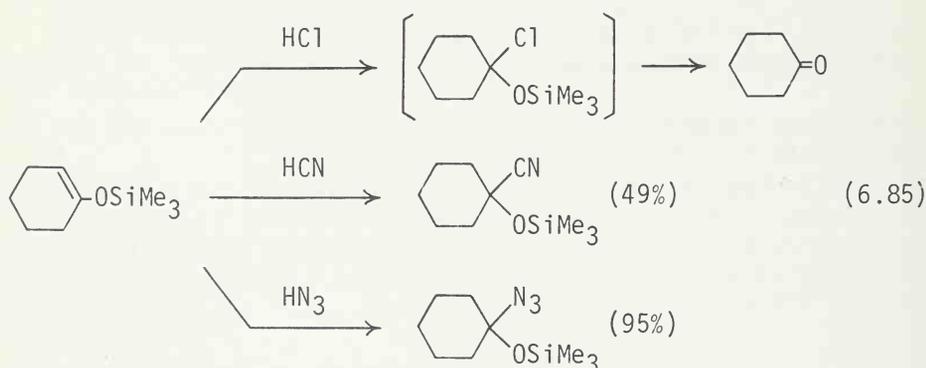


Table 6.9 Reactions of Trialkylsilyl Enol Ethers with Halogens and Halides

Halogen or Halide	Group Y of Product	Ref.
Cl ₂	-Cl	6.64
Br ₂	-Br	6.65
PhSCl	-SPh	6.66
ArSO ₂ Cl	-SO ₂ Ar	6.67
NOCl	=NOH	6.68

It should be noted that all of the reagents listed in Table 6.9 are those that also react readily with more usual C=C bonds. On the other hand, acyl halides and alkyl halides, which react readily with highly ionic enolates but not with usual C=C bonds, do not react readily with silyl enol ethers except for some poly-halogenated derivatives, such as Cl₃CCOCl and NCCCl₃. The reaction with acyl halides can be markedly catalyzed by HgCl₂ (6.69). The products, however, are oxygen-acylated enols.

Reactions with Brønsted Acids The reaction of silyl enol ethers with strong mineral acids generally produces the parent carbonyl compounds via addition-elimination. With some weaker Brønsted acids, such as HCN and HN₃, the addition products can be obtained as isolable compounds (6.59, 6.70).

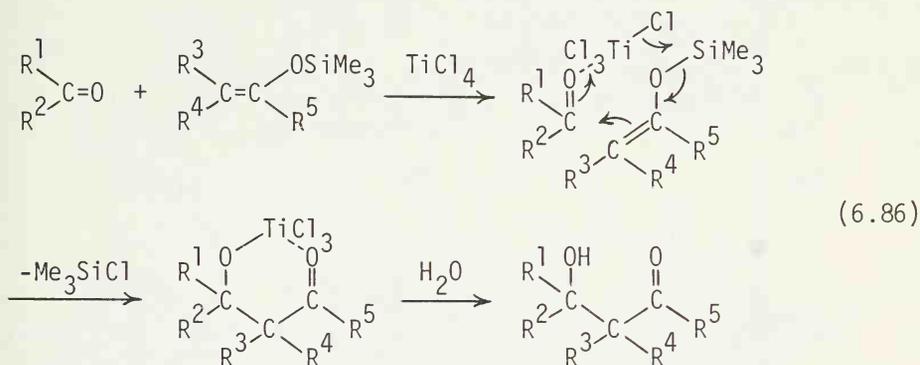


Titanium(IV)-Promoted Reactions Recent extensive investigations of the reactions of silyl enol ethers in the presence of TiCl₄,

conducted mainly by Mukaiyama and his associates, have led to various synthetically useful reactions which amount to the trialkylsilyl-moderated reactions of enolate anions. In general, these reactions provide the following advantages over the conventional enolate anion reactions:

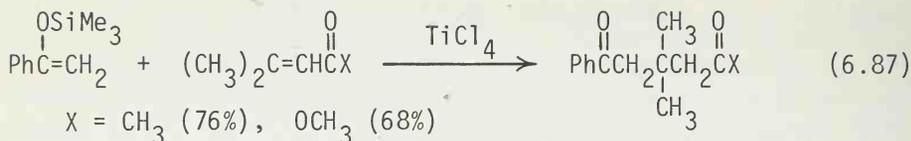
1. The titanium-promoted reactions of silyl enol ethers are generally highly regioselective.
2. Scrambling of two or more reactants does not take place extensively.
3. The titanium-promoted reactions of silyl enol ethers not only exhibit different chemoselectivity patterns but are generally more highly chemoselective than the corresponding enolate anion reactions.

(a) Cross-aldol reaction Aldehydes and ketones undergo a remarkably selective cross-aldol reaction with silyl enol ethers in the presence of TiCl_4 (6.71). The reaction is regioselective. The corresponding reaction of ketone alkyl (trialkylsilyl) acetals gives β -hydroxy esters (6.72). The following scheme has been proposed to account for the role of TiCl_4 (eq. 6.87).



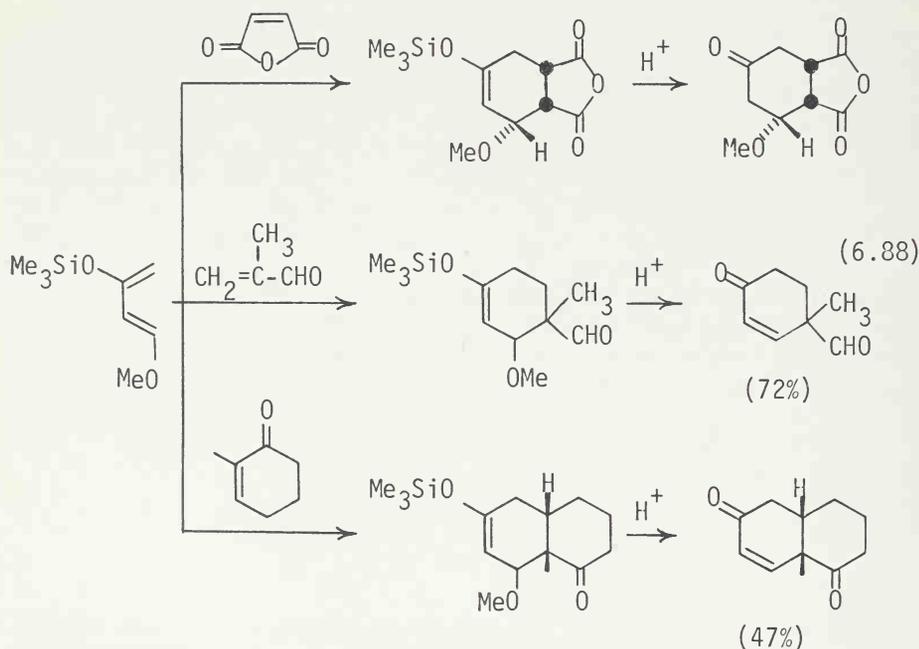
(b) Michael reaction The titanium-promoted reaction of silyl enol ethers with α,β -unsaturated ketones and esters provides a novel procedure for the Michael reaction (6.73), which often appears superior to the conventional base-catalyzed procedures. Various other related titanium-promoted reactions of silyl enol ethers have also been reported by Mukaiyama (6.74).

Cycloaddition Reactions As we have already seen, silyl enol ethers can act as silyloxy-substituted olefins. Therefore, the scope of their chemistry can be as broad as that of the chemistry of olefins, although the number of examples reported to date is



still limited. Even so, it is not possible to discuss all representative types in a book of this nature. Only a few selected examples are discussed here.

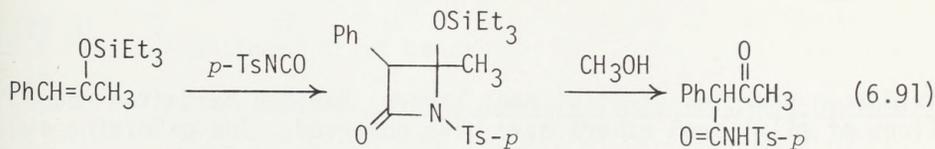
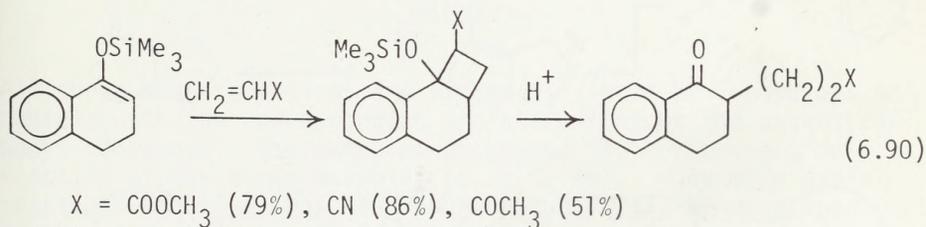
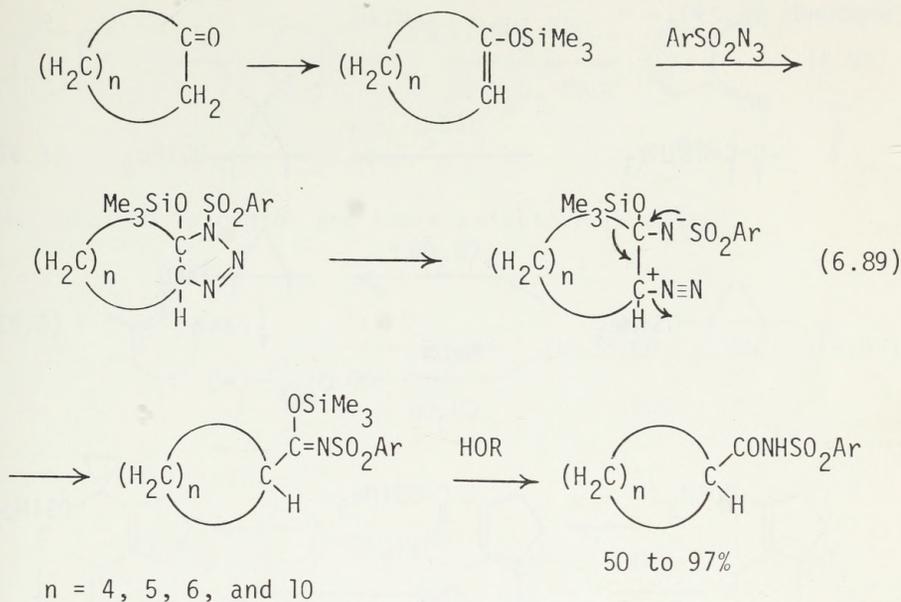
(a) [4+2] Cycloaddition (Diels-Alder reaction) *trans*-1-Methoxy-3-trimethylsilyloxy-1,3-butadiene undergoes facile Diels-Alder reactions, while simultaneously incorporating various functional groups into the products (6.75).



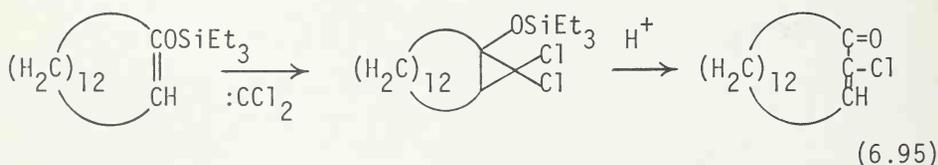
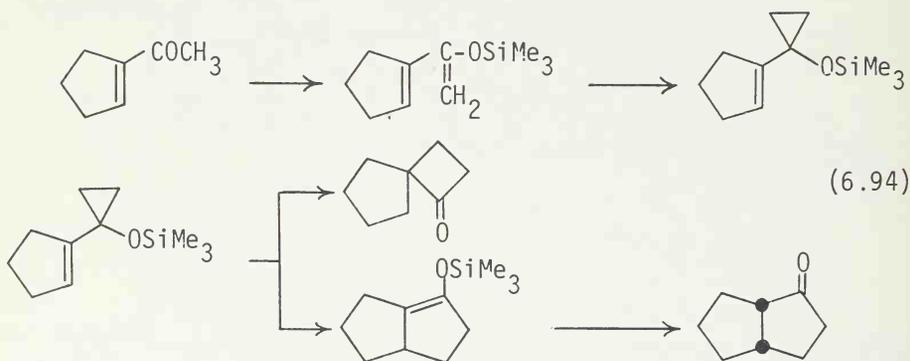
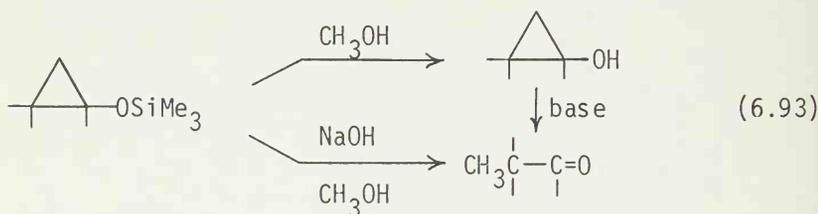
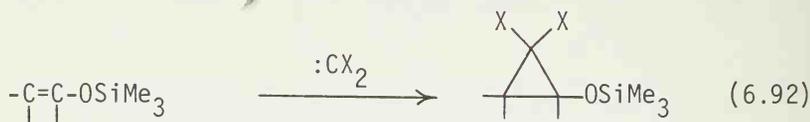
(b) [3+2] Cycloaddition The 1,3-dipolar cycloaddition of arenсульfonyl azides to silyl enol ethers permits a unique ring contraction reaction of cyclic ketones; see eq. 6.89 (6.76).

(c) [2+2] Cycloaddition Triplet-sensitized irradiation of a mixture of a silyl enol ether and a Michael acceptor gives the corresponding [2+2] cycloaddition product which readily hydrolyzes to give the Michael adduct; see eq. 6.90 (6.77).

The reaction of isocyanates with silyl enol ethers gives β -lactams, which readily solvolyze to form β -ketoamides; see eq. 6.91 (6.78).

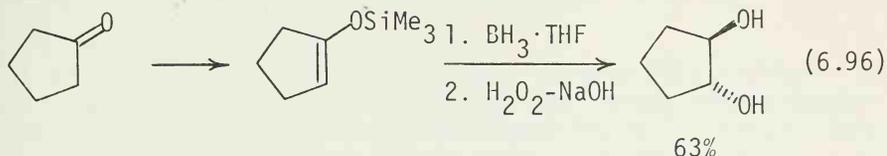


(d) [2+1] Cycloaddition (cyclopropanation) Cyclopropanation of silyl enol ethers via addition of carbenoid reagents provides a facile route to cyclopropanol derivatives which can be converted to a variety of derivatives including α -methylcarbonyl compounds, cyclobutanones, cyclopentanones, and α,β -unsaturated carbonyl compounds (6.79).

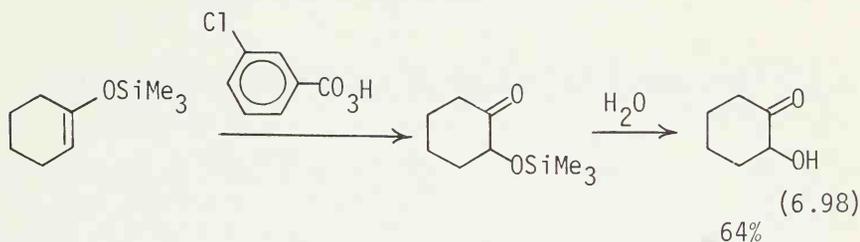
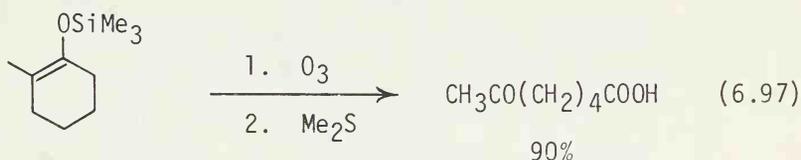


Oxidation Reaction of Silyl Enol Ethers Various oxidation reactions of silyl enol ethers have been observed. The oxidizing agents that have been used include a combination of a boron hydride and alkaline hydrogen peroxide (6.80), singlet oxygen

(6.81), ozone (6.82). A few synthetically useful examples are shown below.



This reaction is regio- and stereoselective (6.80).



All these transformations are either difficult or impossible to achieve with the corresponding enolate anions or the parent carbonyl compounds. The examples discussed above represent only a fraction of the known examples (6.51, 6.59). Many more useful reactions of silyl enol ethers undoubtedly will be developed. It may be said, however, that we are now in a position to understand reasonably well and in many instances even predict the courses of various silyl enol ether reactions.

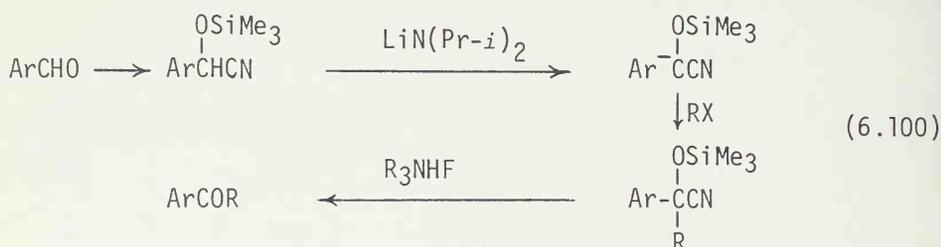
6.4.2.3 α -Functional Silyl Ethers

Trialkylsilyl derivatives of the general structure R_3SiZ , where Z is CH_2CN or CH_2COOEt (6.83), Ar (6.84), CN (6.85), NR_2 (6.86), $NHCOR$ or $N(COR)_2$ (6.87), N_3 (6.88) or SR (6.89), react with

aldehydes and ketones, sometimes in the presence of acid or base catalysts, according to eq. 6.99.



The trimethylsilyl cyanide adducts of ketones can be reduced to β -aminoalcohols, which may be used in the Tiffeneau-Demjanov reaction (6.90). The trimethylsilyl cyanide adducts of aldehydes have been deprotonated to give useful acyl anion equivalents (6.91).



6.4.2.4 Triorganosilyl Groups as Protecting and Volatilizing Agents

One of the first applications of organosilicons to organic synthesis was the conversion of polar organic compounds, such as alcohols and amines, to their more volatile trialkylsilyl derivatives for mass spectral and gas chromatographic analyses and for the protection of active hydrogen-containing functionalities. This subject has been extensively reviewed (6.92), and is not discussed in detail in this book.

The synthetic usefulness of trialkylsilyl groups as protecting agents stems largely from (1) the ease with which the required protected derivatives are formed, (2) their stability in the presence of many carbon nucleophiles (RLi , RMgX , and so on) and oxidizing and reducing agents, and (3) the ease with which they are hydrolyzed with acids, bases, or fluorides.

Until recently, in most instances the trimethylsilyl group had been used. Its hydrolytic instability, however, can cause various difficulties. In order to circumvent such difficulties, various triorganosilyl groups with greater steric requirements have been synthesized and utilized. For example, the approximate relative rates of hydrolysis for a few representative trialkyl groups are as follows: $\text{Me}_3\text{Si}(1) \gg \text{Et}_3\text{Si}(10^{-2}) \gg (\text{t-Bu})\text{Me}_2\text{Si}$

(10^{-4}). Although highly hindered triorganosilyl groups are not readily removed by hydrolysis, they can still be readily removed by the action of R_4NF . The high thermodynamic stability of the Si-F bond (129 kcal/mole) undoubtedly must be responsible for the high efficiency of the fluoride ion.

6.4.3 Reactions of Organotins

As discussed earlier, the bonds to tin are longer and more polarizable than the corresponding bonds to silicon. Thus they can readily participate in a variety of polar reactions. They are also more reactive toward free radicals than the corresponding bonds to silicon. The available data indicate that organotins not only undergo many of those reactions that organosilicons undergo, but also participate in various other reactions. At present, their use in organic synthesis is still considerably more limited than that of organosilicons. It is not inconceivable, however, that in the future organotins might prove more versatile than organosilicons.

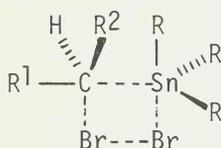
6.4.3.1 Reactions Involving Cleavage of the Sn-C Bond

Polar Substitution Reactions The scope of direct polar substitution reactions of the Si-C bond is very limited. On the other hand, a variety of polar substitution reactions of the Sn-C bond are known. In cases where the Sn-C bond is unactivated, for example, Sn-Et, such reactions appear to involve direct substitution mechanisms proceeding via 6.1 to 6.4 and other related transition states and intermediates. Some of these reactions may also proceed partly or entirely by one-electron transfer processes.

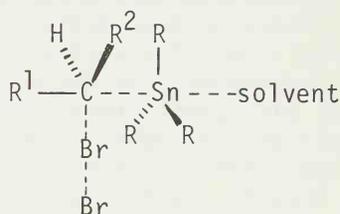
(a) Protonolysis and halogenolysis As mentioned in Sect. 6.4.1, protic acids, but not water or alcohols, and halogens readily cleave even "unactivated" Sn-C bonds (eq. 6.54). These reactions are discussed in detail in various monographs and reviews (6.1, 6.3, to 6.5). They represent some of the most straightforward methods for converting organotins into the corresponding organic compounds. Although protonolysis of the Sn-C bond can be achieved with both acids and bases, the tin-alkyl bonds are quite stable toward alkali. No clear-cut generalization can be made regarding the stereochemistry of protonolysis. Both retention and inversion have been observed.

We have already discussed the fact that certain halogenolysis reactions of organotins might involve at least partly free-

radical processes (eq. 6.45). A recent study (6.93), however, reveals that the brominolysis of some optically active tetraalkyltins proceeds with either partial retention or partial inversion. Thus such a reaction appears to be at least partly polar. It has been tentatively suggested that retention of configuration is probably the main stereochemical course of the brominolysis in methanol and that, in special cases, large steric requirements of the ligands would induce a predominant inversion mechanism. The following transition states have been suggested for the retention reaction.

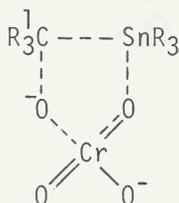


6.27



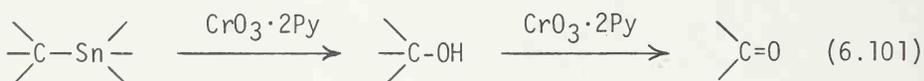
6.28

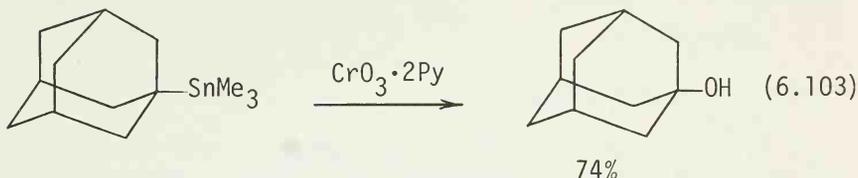
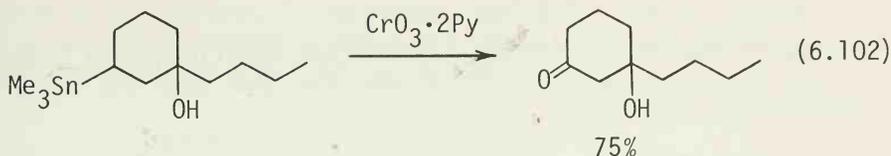
(b) Oxygenolysis of the Sn-C bond Relatively few reactions are known for the conversion of organotins into the corresponding alcohols and carbonyl compounds in part due to the fact that the Sn-C bond is quite resistant to attack by free radicals. Chromic oxide in acetic acid (6.94) and $\text{CrO}_3 \cdot 2\text{Py}$, Py = pyridine (6.38), however, achieve the desired transformation. A cyclic five-center mechanism involving 6.29 has been suggested.



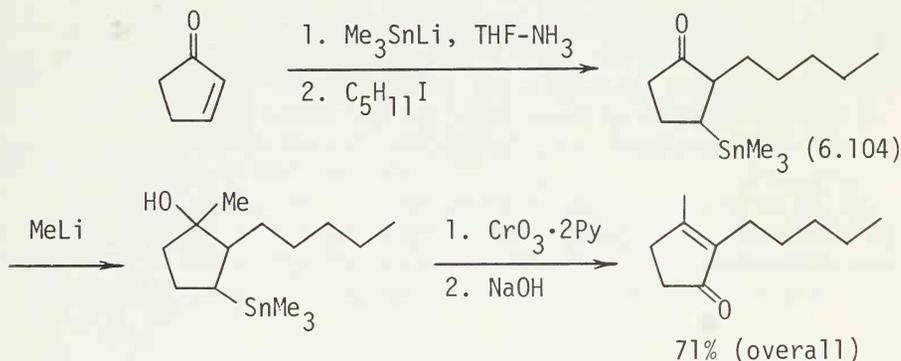
6.29

Secondary and tertiary alkyltins are converted to ketones and tertiary alcohols, respectively, using 10 to 15 equivalents of $\text{CrO}_3 \cdot 2\text{Py}$ (eq. 6.102 to 6.104).





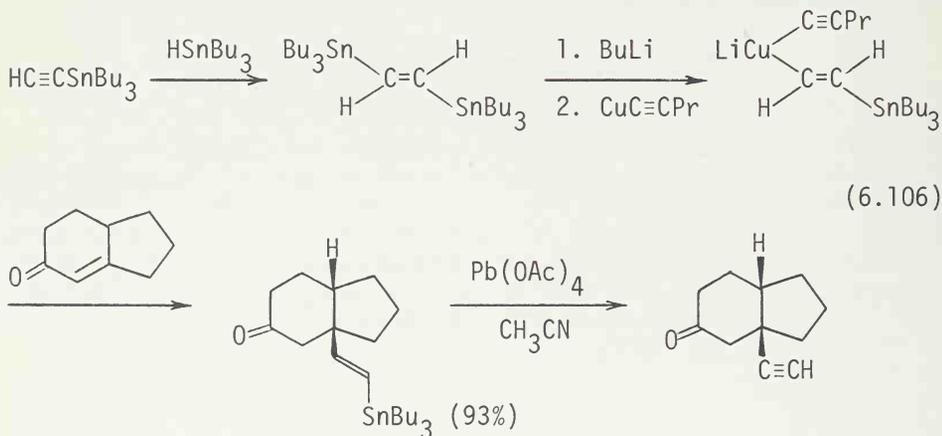
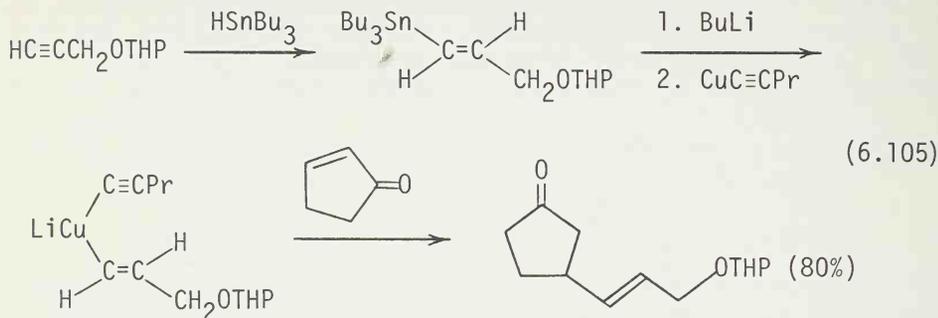
This reaction and the conjugate addition reaction of LiSnR_3 have been utilized in the development of the following dialkylative enone transposition sequence (6.38).



(c) Cleavage of the Sn-C bond via transmetalation. As discussed in Sect. 6.4.1, strongly basic organolithiums readily displace less basic ligands, thereby providing a convenient method for preparing organolithiums, such as those containing allyl, benzyl, alkenyl, aryl, and cyclopropyl groups (6.46). A combination of hydrostannation and transmetalation provides a convenient stereoselective route to olefins and even a route to acetylenes, as shown in eqs. 6.105 and 6.106 (6.35, 6.36).

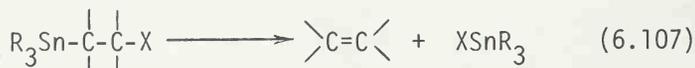
(d) Electrophilic substitution reactions of α,β - and β,γ -unsaturated organotins. These reactions are discussed in Sects. 6.4.1 and 6.4.2. Additional information may be found in a few reviews on these reactions (6.42, 6.95). It may be emphasized

here again that this addition-elimination reaction takes place considerably more readily with organotins than with the corresponding organosilicons.



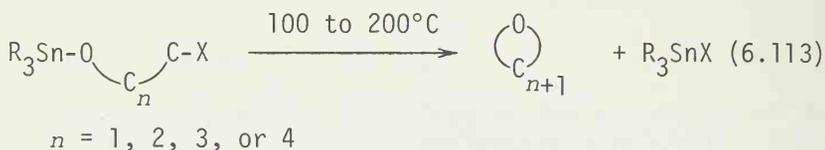
Addition Reactions of Allyltins. Allyltins undergo thermal addition reactions with aldehydes, perhaloketones, and electrophilic olefins and acetylenes (6.95). Although promising, the current scope and synthetic utility of these reactions are rather limited.

Reactions via β -Heterosubstituted Organotins. The high thermodynamic stability of the Sn-O (95 kcal/mole), Sn-Cl (85 kcal/mole), and other Sn-hetero atom bonds suggests that, as in the cases of organosilicons, certain β -heterosubstituted organotins can also undergo facile β -elimination reactions to form olefins.

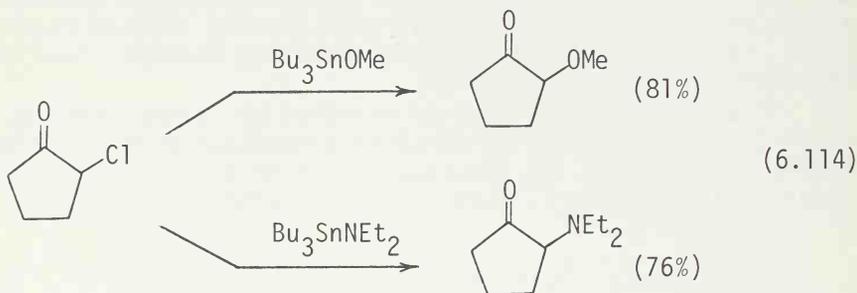


In the following discussion, our attention is mainly focused on those reactions that involve the formation of C-C and C-O bonds.

Intramolecular Reactions. Typical unactivated organotin alkoxides are relatively inert to organic electrophiles, such as organic halides, carbonyl compounds, and epoxides. The intramolecular substitution reaction with organic halides, however, will take place at elevated temperatures; see eq. 6.113 (6.95, 6.97).



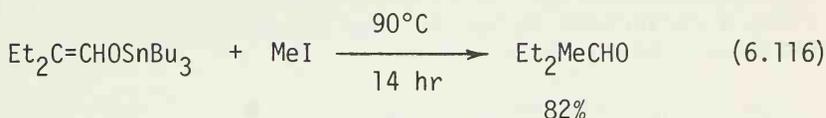
Intermolecular Reactions. (a) Reactions with α -haloketones. The alkoxy and amino derivatives of organotins react with α -chloro-ketones to produce the corresponding α -alkoxy- and α -amino-ketones (6.95, 6.97). The corresponding reaction of α -bromo-ketones is complicated by side reactions.



Since alkali metal alkoxides and amides mainly undergo the Favorskii rearrangement with α -haloketones, the direct substitution reaction of the organotin derivatives appears to be of considerable synthetic value.

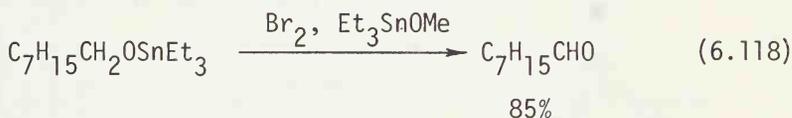
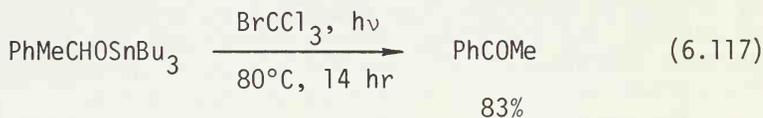
(b) Reactions of triorganostannyl enol ethers. Triorganostannyl enol ethers are more reactive than the corresponding silyl enol ethers. Their synthetic utility, however, has not been well delineated. At elevated temperatures, stannyl enol ethers react with more reactive alkyl halides, such as methyl iodide and allyl bromide (6.95, 6.97). As might be expected, polyalkylation does not occur, although regiochemical scrambling may take place to some extent. This reaction might provide some

advantages over the more classical alkylation reactions with enolate anions.

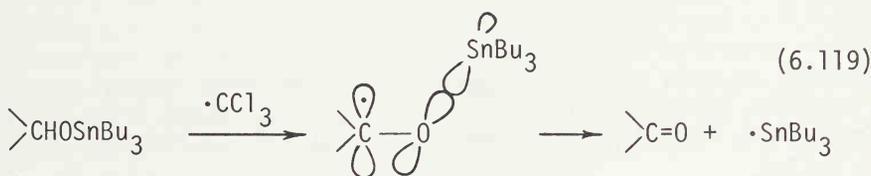


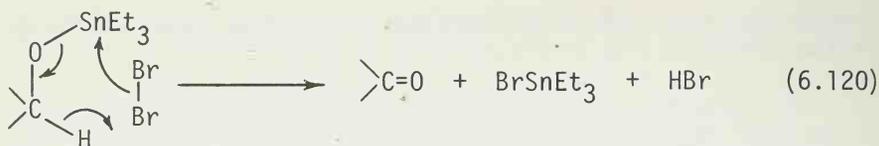
Although not yet well-delineated, the reactions of stannyl enol ethers with carbonyl compounds and electrophilic olefins and acetylenes, under appropriate conditions, might be developed into synthetically useful reactions.

(c) Oxidation of organotin alkoxydes. It has been found that organotin alkoxydes serve as useful intermediates for the oxidation of the corresponding alcohols (6.95, 6.97). A few representative examples follow.

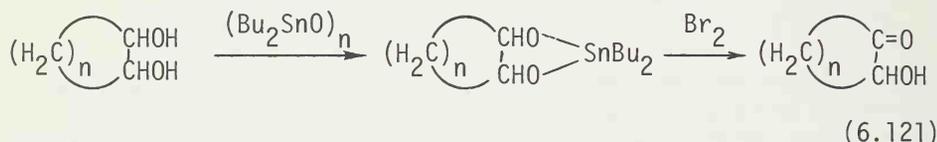


The reaction shown in eq. 6.117 must involve a free-radical mechanism (eq. 6.119), while the reaction with bromine might proceed by a polar cyclic mechanism; see eq. 6.120 (6.98). The use of one equivalent of Et_3SnOMe is necessary to trap HBr .





Regardless of the precise mechanisms involved, it appears certain that these reactions are assisted considerably by the σ - π conjugation effect. The oxidation reaction with bromine has provided a convenient method for the conversion of 1,2-glycols into acyloins; see eq. 6.121 (6.99).

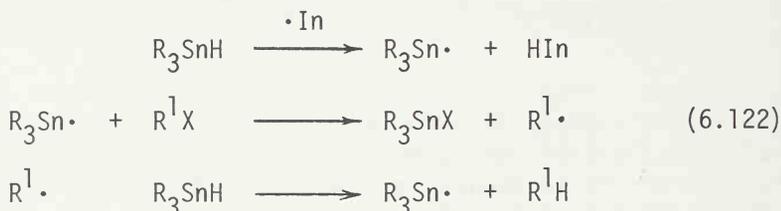


6.4.3.3 Reactions of Organotin Hydrides

The chemistry of organotin hydrides is not discussed in detail here. It has been extensively reviewed by Kuivila (6.100).

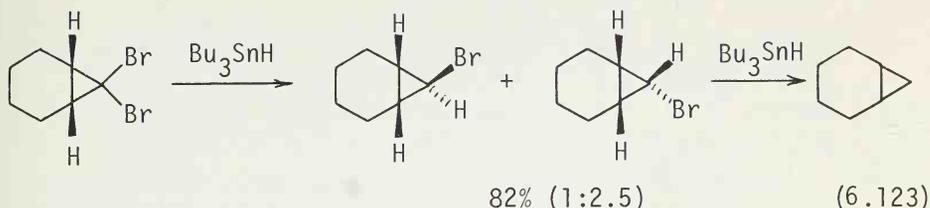
Although a wide variety of functional groups can be reduced by organotin hydrides, the reduction of organic halides and that of olefins and acetylenes (hydrostannation) are the two most important transformations from the viewpoint of organic synthesis. The latter reaction is discussed in Sect. 6.3.3.

The reduction of organic halides has been shown to proceed by the following free-radical mechanism (eq. 6.122).

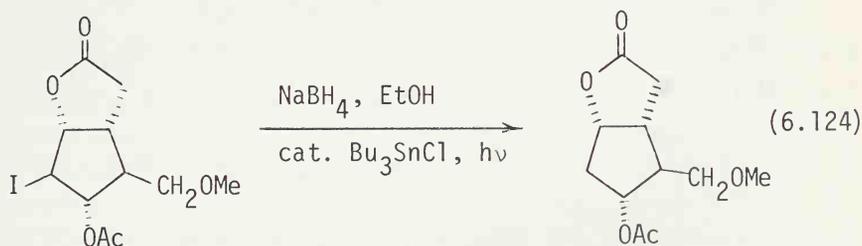


Since most of the reduction reactions of organic halides with Group IIIA metal hydrides proceed by polar mechanisms (Sect. 5.2.3.6), the free-radical reduction with tin hydrides and the polar reduction with Group IIIA metal hydrides are often complementary to each other. In accord with the free-radical mechanism shown above, the reactivity sequence for alkyl bromides is: tertiary > secondary > primary. The facile reduction of tertiary

and secondary alkyl halides is probably the single most important feature of the Sn-H reduction. It is even possible to reduce in a stepwise manner, geminal dibromides first to the monohalides and then to the corresponding hydrocarbons, as shown in eq. 6.123 (6.100).



Various other types of organic halides including alkynyl, allyl, benzyl, alkenyl, and aryl halides can also be reduced, although the Sn-H reduction may not represent the most satisfactory method in these cases. Various unsaturated functional groups other than olefins and acetylenes are also reduced. The reduction of acyl halides is fast, but mixtures of reduced products are usually obtained. Aldehydes react with organotin hydrides at moderate rates to give primary alcohols. On the other hand, ketones, esters, lactones, tertiary amides, and ethers react with trialkyltin hydrides only sluggishly, if at all. Thus these functional groups can be tolerated in the reduction of more reactive functional groups, as shown in eq. 6.124 (6.101).



In this example, the actual reactive species is Bu_3SnH generated in situ by the reaction of NaBH_4 and a catalytic amount of Bu_3SnCl .

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7

ORGANOMETALLICS OF HEAVY MAIN GROUP METALS (Hg, Tl, Pb)

The early chemistry of organomercuries and organothalliums is discussed in textbooks by Coates and Wade (0.6) and by Nesmeyanov and Kocheshkov (0.8). The former also contain a detailed discussion of organolead chemistry. Houben-Weyl's *Methoden der Organischen Chemie* (0.9) contains extensive discussion on these organometallics.

The preparations, structures, and properties of organothalliums and organoleads are also discussed in monographs by Lee (7.1) and by Shapiro and Frey (7.2), respectively. Various reactions of organomercury compounds have been reviewed by Makarova (7.3) and Larock (7.4), and the recent advances in organothallium chemistry have been discussed by Taylor and McKillop (7.5) and by Lee (7.6).

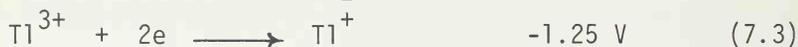
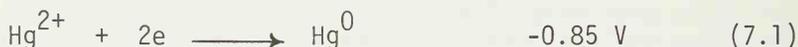
7.1 GENERAL CONSIDERATIONS

7.1.1 Some Fundamental Properties of Mercury, Thallium, and Lead and the Bonds to These Elements

Mercury, thallium, and lead are all relatively electronegative, the electronegativity values for these elements being approximately 1.9 (1.1), 1.8 (1.1), and 1.8 (7.7), respectively (Appendix II). Thus the bonds between these elements and carbon are highly covalent. As a result, even though the M-C bonds, where M = Hg, Tl, and Pb, are polarized such that the carbon atom

assumes some carbanion character, the intrinsic nucleophilicity of these M-C bonds is very low. These heavy elements and the bonds to these elements, however, are highly polarizable. The Hg-X, Tl-X, and Pb-X bonds, where the X group is highly electronegative, for example, F, NO₃, ClO₄, can behave as highly ionic bonds. Thus, for example, organomercurials of the RHgX type containing the highly electronegative X group tend to be more soluble in water than in nonpolar solvents. These highly polarizable ("soft") bonds react readily with "soft" organic substrates, such as olefins, acetylenes, and aromatic compounds (heterometallation). Thus compounds containing these bonds are good electrophiles. This ability to interact readily with soft nucleophiles is one of the most significant properties of compounds containing Hg, Tl, and Pb, and permits a unique and facile entry into organometallics containing these metals.

Another significant feature associated with these elements is the ease with which compounds containing these elements undergo redox reactions involving two oxidation states, as shown in eqs. 7.1 to 7.4 (7.8).



As the oxidation potentials for these reactions indicate, Pb(IV), Tl(III), and Hg(II) are all good oxidizing agents, the relative oxidizing ability being: Pb(IV) > Tl(III) > Hg(II). Although the reduction of organomercuries usually requires suitable reduction agents, organothalliums of the RTl(III)X₂ type and organoleads of the RPb(IV)X₃ type tend to be quite unstable and usually decompose spontaneously. The spontaneous or nucleophile-assisted two-electron transfer process which RTlX₂ and RPbX₃ undergo may be represented by eqs. 7.5 and 7.6.



R¹ may be the same as R²; Y = added nucleophile or X

In addition to the intrinsic instability of $R^1Tl(III)X_2$ and $R^1Pb(IV)X_3$, the thermodynamically stable nature of $Tl(I)X$ and $Pb(II)X_2$, where X = electronegative groups such as halogen, OR, OOCR, and so on, must also be providing a driving force for these reactions. A highly intriguing aspect of these decomposition reactions is that $R^1Tl(III)X_2$ and $R^1Pb(IV)X_3$ are now acting as sources of carbocations and/or carbocationic species. This property is unique only to a relatively small number of heavy metals, such as Tl, Pb, and Pd.

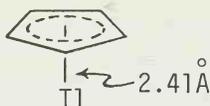
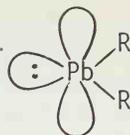
The Hg-C, Tl-C, and Pb-C bonds are thermodynamically rather weak, the bond energy values for these bonds, where the carbon group is a simple alkyl group, being approximately 50, 25 to 30, and 30 kcal/mole, respectively. Therefore, these organometallics should, in principle, be good sources of carbon-free radicals. Indeed, organomercuries and organoleads have acted as efficient sources of carbon-free radicals. On the other hand, organothalliums usually participate only in two-electron transfer processes. This is presumably due to the fact that thallium (II) is highly unstable with respect to disproportionation to thallium(III) and thallium(I).

Finally, although not yet fully exploited, it appears potentially significant to note that the weak and highly polarizable nature of the M-C bonds, where $M = Hg$ and Pb , renders these bonds some of the most effective participants in σ - π conjugation, as discussed in Sect. 6.4.1. It appears almost certain that many additional synthetic capabilities based on these unique properties of heavy metals await future exploration.

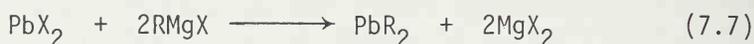
7.1.2 Structural Aspects

As already discussed, Hg, Tl, and Pb all can exist in two stable oxidation states in addition to the neutral oxidation state. There is one significant aspect to be pointed out. Whereas a number of inorganic derivatives of Hg, Tl, and Pb, in which the metal atoms exist in the lower oxidation state, that is, Hg(I), Tl(I), and Pb(II), are known as isolable species, there are relatively few compounds that contain the Hg(I)-C, Tl(I)-C, and Pb(II)-C bonds. Organothallium(I) compounds, in which the Tl(I)-C is largely covalent, do not appear to have been isolated. Cyclopentadienylthallium (7.1) and its derivatives, in which the Tl(I)-C is believed to be largely ionic, are the only group of organothallium(I) compounds known to date as isolable species (7.5b, 7.6).

Diorganolead(II) compounds are carbene analogs, and the probable structure of the singlet species may be represented by 7.2.

7.17.2

It is generally assumed that diorganoleads are formed as intermediates in the preparation of tetraorganoleads by the reaction of PbX_2 with organometallic compounds (eq. 7.7).

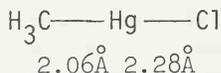


In general, diorganoleads are highly unstable (7.2). As mentioned in Sect. 6.2, however, certain diorganoleads containing bulky ligands have been obtained and characterized (6.20). Although they represent an interesting class of organometallics, their utility in organic synthesis remains to be explored.

It follows from the discussion presented above that the great majority of organomercuries, organothalliums, and organoleads contain Hg(II), Tl(III), and Pb(IV).

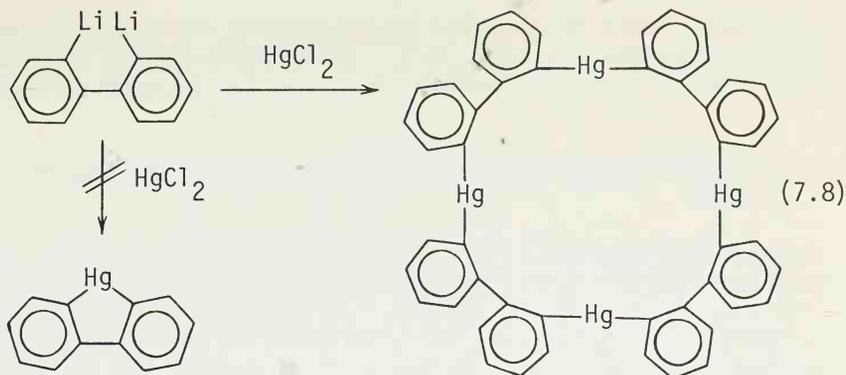


Both RHgX and R₂Hg exist as linear or nearly linear species, for example, 7.3, in which the mercury atom utilizes the *sp* hybridized orbitals for bonding. This tendency to form linear

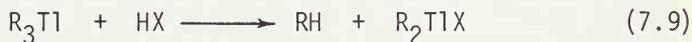
7.3

molecules is so strong that the formation of common rings containing one or more mercury atoms is quite unfavorable, as indicated by the following example; see eq. 7.8 (7.9).

Organothallium(III) compounds share many of the structural features with organometallics of the lower members of the Group IIIA elements (Sect. 5.2.1). Thus many of them exist as monomeric trigonal planar species, whereas others exist as bridged dimers and polymers. The main point of interest here is that RTlX₂,

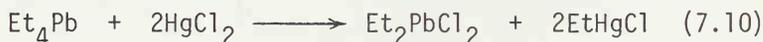


R_2TlX , and R_3Tl differ vastly in their thermal and chemical stability. As discussed earlier, monoorganothallium(III) compounds are thermally quite labile. On the other hand, diorganothallium(III) derivatives are both thermally and chemically quite stable. They are not readily attacked by water and oxygen. Triorganothalliums can readily be protonolyzed by various reagents, such as HCl, water, alcohols, and thiols, in most cases producing diorganothallium derivatives; see eq. 7.9 (7.6).



Although a number of species represented by R_3Tl and R_2TlX are now known (7.6), the very limited nature of their application in organic synthesis does not warrant a detailed discussion of these species here.

The most important application of organoleads by far is the use of tetraorganoleads as antiknock agents, despite the current effort to curtail this application. Tetraorganoleads are also used in the preparation of organomercury fungicides, as shown in eq. 7.10.



Other than these commercial applications, relatively little is known about the usefulness of R_4Pb , R_3PbX , and R_2PbX_2 in organic synthesis. On the other hand, monoorganolead(IV) derivatives ($RPbX_3$) have been postulated as intermediates in a number of oxidation reactions of organic compounds with $Pb(OAc)_4$, as discussed later. As to the structures of these organolead compounds, suffice it to say that organolead compounds share many of the

structural features with the corresponding organotin compounds briefly discussed in Sect. 6.2. Interested readers are referred to the monographs and reviews cited earlier (0.6, 0.9, 7.2, 7.3).

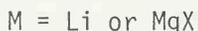
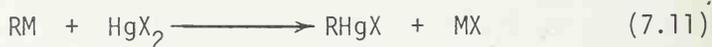
7.2 PREPARATION OF ORGANOMERCURIES, ORGANOTHALLIUMS, AND ORGANO-LEADS

As in many other cases, transmetallation (Method XI) represents by far the most general method for the synthesis of organometallics containing Hg, Tl, and Pb. On the other hand, heterometallation (Method VII), especially oxymetallation, provides a unique and convenient route to these organometallics. Closely related to this method is the metal-hydrogen exchange reaction (Method V), which provides a direct route to the arylmetals containing mercury and thallium. While these three reactions represent the most convenient laboratory methods, the reaction of organic halides with metal alloys (Method I) is by far the most significant industrial method for preparing organoleads (7.2). This so-called "alloy method" is also applicable to the preparation of organomercuries (7.10), and organothalliums (7.1). In the presence of light, highly reactive organic iodides, such as those containing the methyl, methylene, benzyl, allyl, and propargyl groups, react with metallic mercury to produce the corresponding organomercuric iodides (7.10). Organic bromides and chlorides, however, are generally unreactive.

7.2.1 Transmetallation

7.2.1.1 Organomercuries

The reaction of organolithiums and Grignard reagents with mercuric halides produces either organomercuric halides or diorganomercuries (eqs. 7.11 and 7.12).



Although generally less useful, various other polar organometallics, such as those containing Na, K, Zn, and Al, have also been used in this reaction. For example, various polyhalomethylmer-

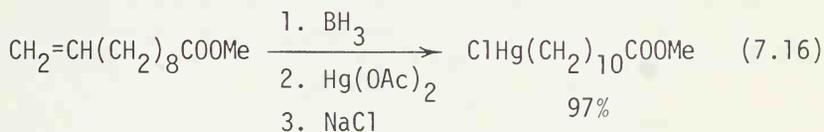
cury derivatives, which have proven to be valuable divalent carbon transfer agents (7.11), are readily obtained by the following reaction (eq. 7.13).



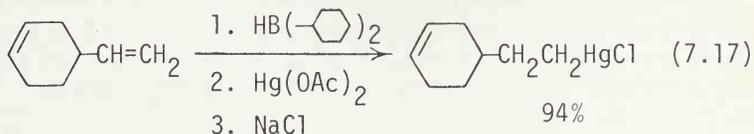
The reaction of organoboranes with mercuric salts has recently been developed into a valuable route to organomercuries (7.12). Primary trialkylboranes, readily available via hydroboration of terminal olefins (Sect. 5.2.2.2), undergo a rapid reaction with $\text{Hg}(\text{OAc})_2$ at room temperature to produce alkylmercuric acetates (7.13), which are readily convertible to the corresponding alkylmercuric chlorides by treatment with aqueous sodium chloride.



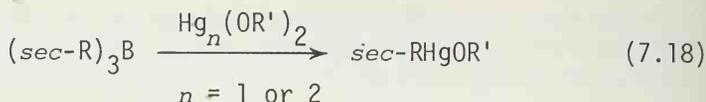
It is important to note that various functionally substituted alkylmercury compounds are obtained by this method, as shown in eq. 7.16.



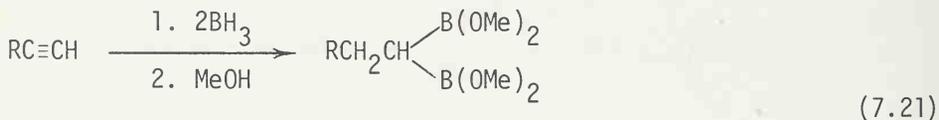
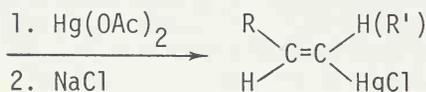
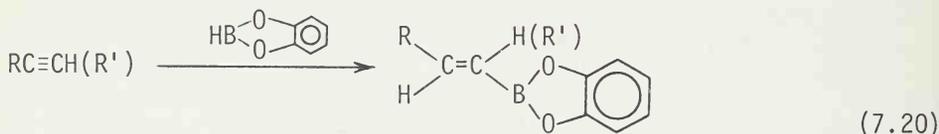
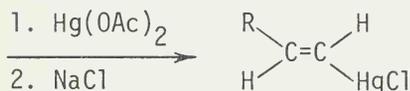
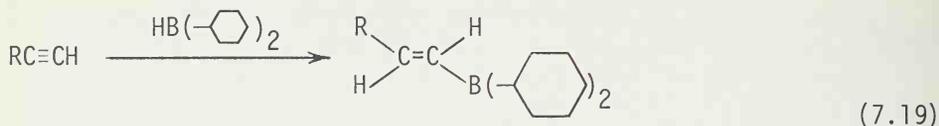
Secondary alkyl-boron bonds do not react with mercuric salts under the same conditions. Thus they can serve as useful "dummy" groups allowing various selective transformations, as shown in eq. 7.17.



Secondary alkylmercury compounds can, however, be prepared by the reaction of secondary alkylboranes with mercury alkoxides (7.14).



Alkynes can be converted to either alkenylmercuries or *gem*-dimercurialkanes (7.15).

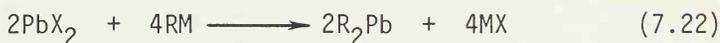


Whereas internal alkynes can be nicely converted to the corresponding alkenylmercuric chlorides by the catecholborane procedure (eq. 7.20), the corresponding reaction of alkenyldicyclohexylboranes is complicated by a competitive side reaction involving the 1,2-migration of the cyclohexyl group.

7.2.1.2 Organothalliums and Organoleads

Organothalliums of the R_3Tl and R_2RlX types (7.1, 7.6) and organoleads of the R_4Pb type (7.2) can readily be prepared by the

transmetallation reaction via organolithiums and Grignard reagents, while partially organosubstituted lead compounds of the R_3PbX and R_2PbX_2 types are most commonly prepared via R_4Pb (7.2). Although the limited usefulness of these compounds in organic synthesis does not permit detailed discussion of this subject, one peculiar aspect of organolead chemistry may be mentioned here. The inorganic salts of the divalent lead are generally more stable and easier to handle than those of the tetravalent lead, whereas diorganoleads are much less stable than tetraorganoleads. Furthermore, diorganoleads readily decompose to the corresponding tetraorganoleads and metallic lead. The ease with which inorganic divalent lead compounds (PbX_2) can be handled and the fact that R_2Pb can be converted readily into R_4Pb make the following method involving the use of PbX_2 often more convenient than the corresponding reaction of PbX_4 (7.2).



7.2.2 Oxymetallation and Related Heterometallation Reactions

7.2.2.1 Oxymercuration

Mercuric salts, such as $Hg(OAc)_2$ and $Hg(OOCCF_3)_2$, react with olefins and acetylenes in the presence of active hydrogen compounds (HY) to produce a variety of β -heterosubstituted organomercuries (eq. 7.23).



The reaction not only provides a highly convenient route to organomercuries, but also permits the Markovnikov functionalization of olefins (Sect. 7.3.2.1).

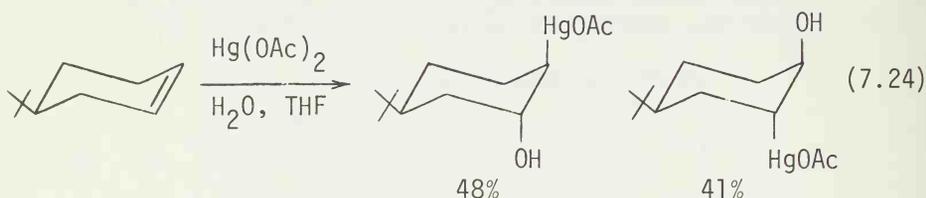
Scope, Regiochemistry, and Stereochemistry. The scope, regiochemistry, and stereochemistry of the oxymercuration reaction have been examined extensively (2.27). The available data indicate the following:

(1) Although certain highly hindered olefins fail to give oxymercured products, various mono-, di-, tri-, and tetrasubstituted olefins have participated in the reaction.

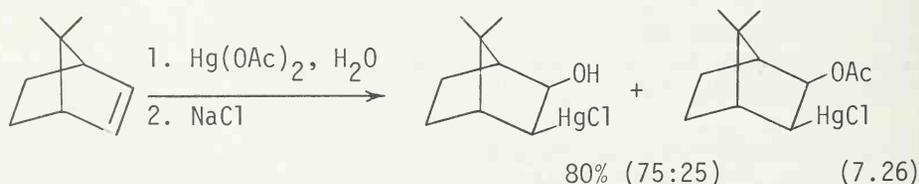
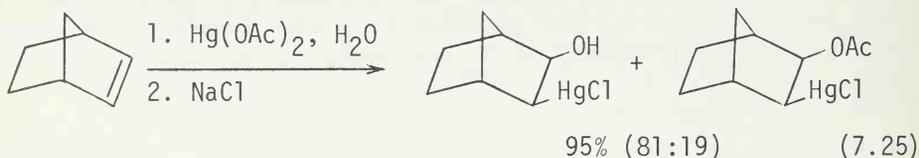
(2) The rates of oxymercuration generally decrease in the order: $R_2C=CH_2 > RCH=CH_2 > cis-RCH=CHR > trans-RCH=CHR > R_2CH=CHR > R_2C=CR_2$ (2.27, 7.16). It is clear that the reactivity order is governed by both steric and electronic effects.

(3) Oxymercuration proceeds such that, after replacement of the mercury-containing group with a hydrogen atom, the Markovnikov addition products are obtained exclusively or predominantly (2.27, 7.16).

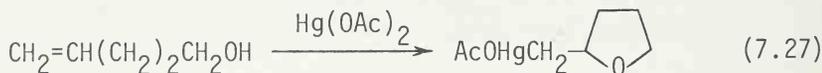
(4) The reaction with unstrained olefins generally involves a *trans* addition, as shown in eq. 7.24 (7.17, 7.18). It should be noted that conformationally rigid cyclohexenes, such as 4-*tert*-butyl-1-cyclohexene, give almost exclusively the axially disubstituted products (7.18).

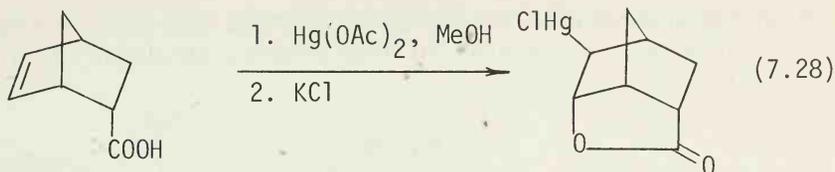


Certain strained olefins, such as norbornene and 7,7-dimethylnorbornene, give *cis*-addition products, as shown in eqs. 7.25 and 7.26 (7.17, 7.18). Particularly interesting is the nearly exclusive formation of the *cis*-*exo* products even in the case of 7,7-dimethylnorbornene.

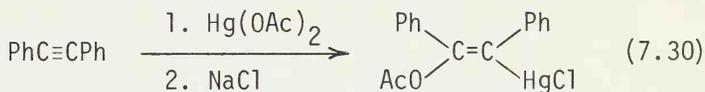
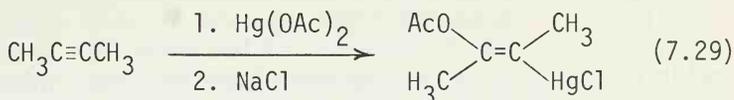


(5) Oxymercuration of olefins containing suitably located nucleophilic groups results in cyclization (7.21, 7.22).





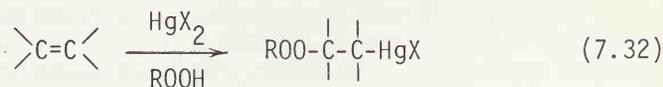
(6) Oxymercuration of acetylenes produces β -oxyalkenylmercury derivatives. The stereochemistry of the products seems to depend on both the nature of substituents and the reaction conditions (7.23, 7.24).



(8) The most commonly employed nucleophile is water. Other oxy nucleophiles, however, can also be used. Using alcohols as solvents, β -alkoxyorganomercury compounds have been obtained; see eq. 7.31 (7.25).

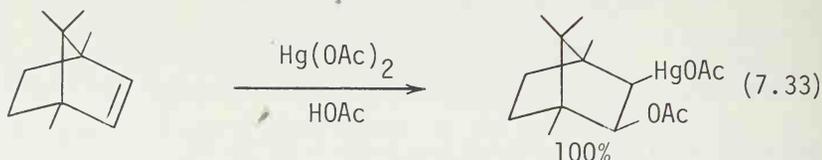


Mercuric trifluoroacetate, $\text{Hg(O}_2\text{CCF}_3)_2$, appears to be superior to Hg(OAc)_2 in this reaction (7.25). Peroxymercuration has also been achieved using hydrogen peroxide (7.26, 7.27) and alkylhydroperoxides (7.27, 7.28). Although Hg(OAc)_2 has been commonly used, $\text{Hg(O}_2\text{CCF}_3)_2$ also appears to be a superior reagent in this reaction (7.29).

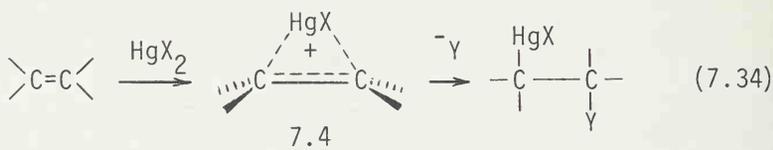


Formation of esters via oxymercuration has already been mentioned. By using Hg(OAc)_2 , either in the absence of a protic solvent

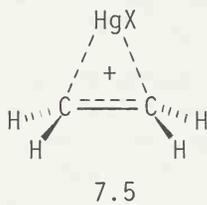
or in the presence of acetic acid, olefins can be converted to the corresponding acetates in high yields, as shown in eq. 7.33 (7.19b).



Mechanism of Oxymercuration. The mechanism of the oxymercuration reaction is still not very clear. It is conceivable that more than one mechanism might operate in this reaction. The trans oxymercuration reaction, which generally proceeds without being accompanied by the Wagner-Meerwein rearrangement, has been interpreted by many workers in terms of the intermediacy of mercurinium ions (7.4) as shown in eq. 7.34.

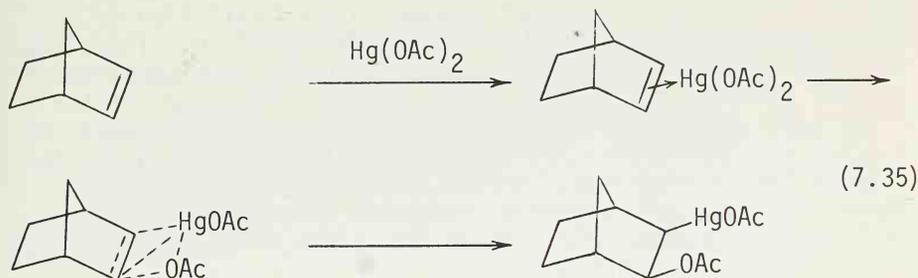


Spectroscopic data indicating the existence of the ethylenemercurinium ion (7.5) in $\text{FSO}_3\text{H-SbF}_5\text{-SO}_2$ have recently been presented (7.30).

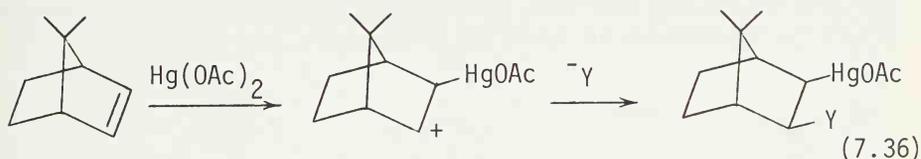


On the other hand, the cis oxymercuration reaction observed with certain strained olefins, such as norbornene and 7,7-dimethylnorbornene, is not consistent with the above mechanism. Several mechanisms proposed by various workers are reviewed by Traylor (2.28), who suggested that the cis oxymercuration reaction might proceed through a concerted molecular addition, as shown in eq. 7.35. It appears difficult, however, to accommodate the results observed with 7,7-dimethylnorbornene by this mechanism, since certain addition reactions that are known to proceed by concerted molecular addition mechanisms, such as hy-

droboration, have been shown to produce predominantly the endo isomers (7.31).



On the other hand, the stereochemical results observed with both norbornene and 7,7-dimethylnorbornene can be accommodated by the open carbonium ion mechanism proposed by Brown (7.32). This mechanism assumes that the attack of an olefin by an electrophile which can take place at one end of the C=C bond is not hindered by the presence of the *syn*-7-methyl group (eq. 7.36).



What this mechanism fails to explain convincingly is the fact that the reaction is not complicated by the Wagner-Meerwein rearrangement, although it is not necessarily inconsistent with the mechanism. At this point, we must conclude that the mechanism of oxymercuration still remains a subject of controversy. Additional information on this subject can be found in a few recent reviews of the mechanism of oxymercuration (0.10, 2.27, 2.28).

7.2.2.2 Other Heteromercuriation Reactions

Various nucleophiles other than the oxy nucleophiles have been used in the heteromercuriation reaction. Aminomercuriation can be achieved using amines (7.33), acetonitrile (7.34), sodium azide (7.35), and sodium nitrite (7.36).

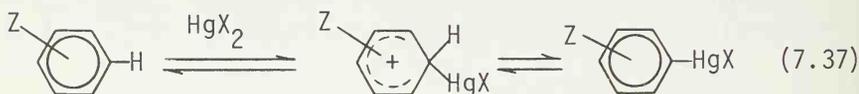
Halomercuriation of olefins appears to be a thermodynamically unfavorable process. Certain acetylenes, however, have been converted to *trans*- β -chloroalkenylmercury derivatives, as discussed in Sect. 2.7.

7.2.2.3 Oxythallation and Oxyplumbation

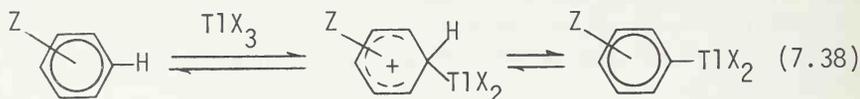
As mentioned in Sect. 2.7, several other heavy metals, such as Tl, Pb, Pd, and Pt, also participate in oxymetallation (2.27). Oxypalladation and oxyplatination are discussed in a later chapter (Sect. 10.3). Although oxythallation and oxyplumbation represent the most convenient routes to organothalliums of the $RTlX_2$ type and organoleads of the $RPbX_3$ type, respectively, these species are generally unstable and tend to decompose under the oxymetallation conditions without permitting their isolation. These reactions are therefore discussed in a later section of this chapter dealing with various reactions of organometallics containing Hg, Tl, and Pb.

7.2.3 Metal-Hydrogen Exchange -- Mercuration and Thallation of Aromatic Compounds

The reaction of olefins and acetylenes with mercuric salts in the presence of appropriate protic nucleophiles (HY) gives addition products, as discussed in the preceding section. On the other hand, the corresponding reaction of arenes usually undergoes the following addition-elimination reaction (metal-hydrogen exchange) to produce arylmercury compounds; see eq. 7.37 (7.10).



Thallium salts, such as $Tl(OAc)_3$ and $Tl(O_2CCF_3)_3$, also undergo a closely related reaction; see eq. 7.38 (7.5, 7.6).



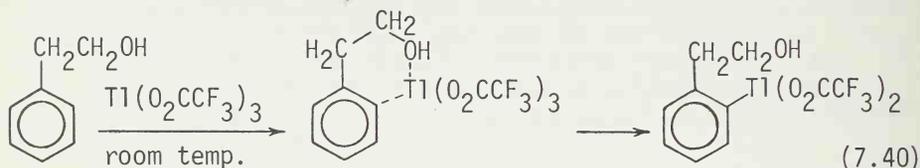
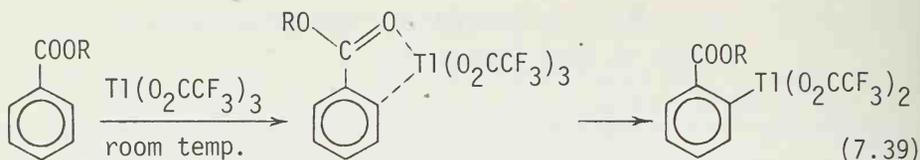
They are facilitated by highly ionic mercury and thallium salts, such as $Hg(O_2CCF_3)_2$ and $Tl(O_2CCF_3)_3$.

These reactions exhibit the characteristics of typical electrophilic aromatic substitution reactions. Thus the difficulties and limitations associated with the electrophilic aromatic substitution reactions have been encountered. These reactions often result in mixtures of *o*-, *m*-, and *p*-isomers, and deactivated aromatic compounds fail to undergo these reactions. The regiochemistry of the thallation reaction is summarized in Table 7.1 (7.37).

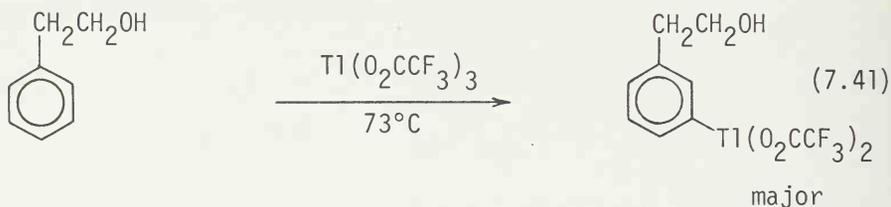
Table 7.1. Regiochemistry of the Thallation of Aromatic Compounds at Room Temperature

Z	Isomer Distribution, (%)		
	<i>o</i>	<i>m</i>	<i>p</i>
Me	9	4	87
Pr- <i>i</i>	1	5	94
OMe	7	-	93
CH ₂ OMe	>99	-	-
CH ₂ CH ₂ OMe	85	3	12
(CH ₂) ₃ OMe	27	6	67
CH ₂ OH	>99	-	-
CH ₂ CH ₂ OH	83	6	11
OAc	21	-	79
CH ₂ OAc	50	21	29
CH ₂ CH ₂ OAc	3	13	84
COOH(or COOMe)	95	5	0
CH ₂ COOH(or CH ₂ COOMe)	92	3	5
CH ₂ CH ₂ COOH	29	13	58
CH ₂ CH ₂ COOMe	53	7	40

The results summarized in Table 7.1 indicate the following: (1) Simple alkyl groups direct the thallium-containing group mainly to the para position. (2) When a substituent contains a nucleophilic moiety in such a position as to permit either a five- or a six-membered (but not four-membered) transition state, as shown in eqs. 7.39 and 7.40, the *o*-isomers tend to dominate the product mixtures.



Since deactivated aromatic compounds are very reluctant to participate in the thallation reaction, *m*-substituted aryl-thalliums are seldom obtained as major products under kinetic conditions. By taking advantage of the reversible nature of the thallation reaction, however, the *m*-isomers can be obtained as major products under equilibrating conditions, as shown in eq. 7.41.



7.3 REACTION OF ORGANOMERCURIES

At present, there are four major uses of organomercuries in organic synthesis in the laboratories: (1) hydration and related reactions of olefins via heteromercuriation-demercuration, (2) carbenoid transfer reactions, (3) transmetalation reactions producing more reactive organometallics, and (4) reactions of α,β -unsaturated organomercuries with electrophiles. There are, of course, many other reactions of organomercuries. Most of them, however, either are not unique to mercury or are not very useful from the viewpoint of organic synthesis. Before discussing the four above-mentioned reactions, some general methods for the cleavage of the Hg-C bond are discussed.

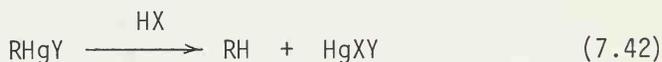
7.3.1 Cleavage of the Hg-C Bond

7.3.1.1 Reactions with Carbon Electrophiles

The highly covalent nature of the Hg-C bonds makes them poor nucleophiles. Indeed, unactivated Hg-C bonds are generally unreactive toward typical organic electrophiles, such as organic halides, carbonyl compounds, and epoxides.

7.3.1.2 Protonolysis and Halogenolysis

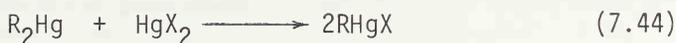
Certain inorganic electrophiles, such as proton acids and halogens, readily react with various types of organomercuries to produce organic products via cleavage of the Hg-C bond (eqs. 7.42, 7.43). These reactions have been thoroughly reviewed by Jensen and Rickborn (7.38).



The Hg-C bonds are generally stable to water and alcohols. Thus the protonolysis of these bonds requires stronger acids, such as HCl and H₂SO₄. Carboxylic acids are much less effective. In general the acid cleavage of dialkylmercuries occurs much more readily than the corresponding reaction of alkylmercuric salts. The Hg-aryl bonds are cleaved more readily than the Hg-alkyl bonds, the order of decreasing ease of cleavage by HCl being: anisyl > tolyl > phenyl > chlorophenyl > methyl > *n*-butyl > isoamyl > benzyl > cyclohexyl. The stereochemistry of the protonolysis of the Hg-C bond is not very clear. The available data, however, indicate that retention is the preferred course.

It may be pointed out here that the Hg-C bond is not cleaved readily by alkalis or other common bases.

Halogenolysis of the Hg-C bond is also a highly general reaction which takes place with all halogens (7.38). Although dialkylmercuries appear more reactive than the corresponding alkylmercuric salts (RHgY), it is difficult to make a definitive generalization due to a rapid competing side reaction shown in eq. 7.44.

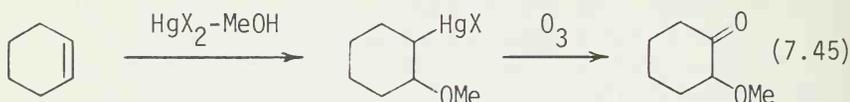


While the reaction of *cis*- or *trans*-4-methylcyclohexylmercuric bromide with bromine in pyridine proceeds with 100% reten-

tion, the corresponding reaction in CCl_4 or CS_2 involves essentially complete loss of configuration. The available information indicates that the halogenolysis of the Hg-C bond can proceed by both polar and free-radical mechanisms (7.38).

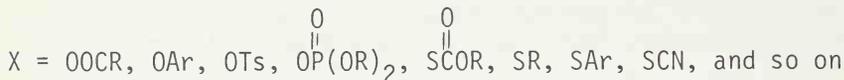
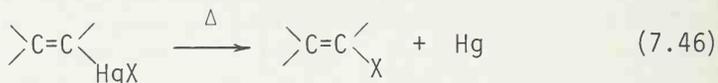
7.3.1.3 Oxidation and Reduction

The Hg-C bond is generally quite stable toward oxygen. On the other hand, organomercuries can readily be oxidized by ozone. Secondary alkylmercuries give good yields of ketones, while primary alkylmercuries are converted to mixtures of carboxylic acids (7.39). The following oxymercuration-ozonation sequence has been developed as a method for the conversion of olefins to α -oxy ketones (eq. 7.45).



In general, the Hg-C bond is stable toward many other oxidizing agents, such as CrO_3 .

The oxidation of the alkenyl group bonded to mercury can readily be achieved by thermolysis, shown in eq. 7.46 (7.4, 7.40). This is a redox reaction in which the mercury is reduced to metallic mercury.

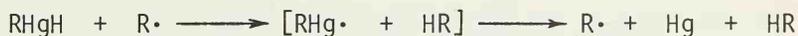


Although the reaction is nonstereospecific, it appears to be of some synthetic utility, and might be compared with a related transformation involving alkenylsilicon compounds (Sect. 6.4.2.1).

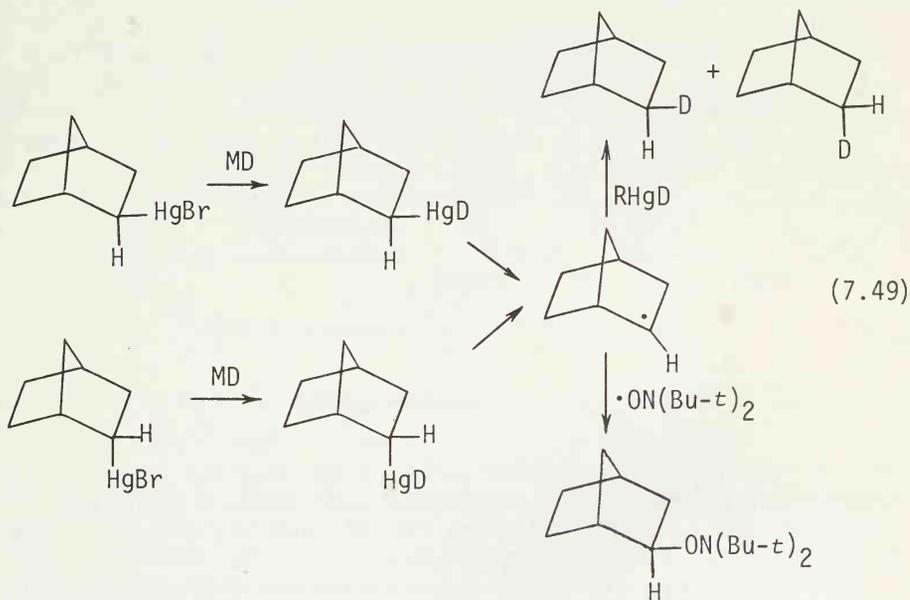
In contrast to the oxidation of the Hg-C bond, its reduction is a facile process. A variety of reducing agents including LiAlH_4 , NaBH_4 , Na/Hg , and RNH_2 (7.4) have been used to convert organomercuries into the corresponding hydrocarbons.



Ready availability and high selectivity make NaBH_4 the reagent of choice. The reaction of organomercuries with NaBH_4 usually produces reduced products in high yields. The reduction of alkylmercuric halides with NaBH_4 appears to proceed via the corresponding alkylmercuric hydrides which decompose to alkanes and metallic mercury by a free-radical mechanism (7.41). One plausible mechanism is shown in eq. 7.48.



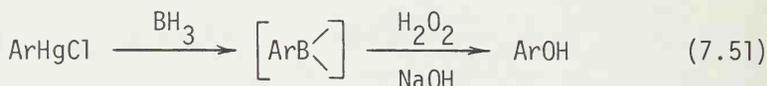
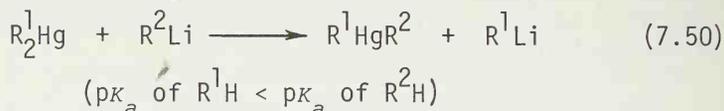
In accord with the above free-radical mechanism, both exo- and endo-2-norbornylmercuric bromides react with NaBD_4 , Et_2AlD , $\text{CuD}\cdot\text{PBu}_3$, or Bu_3SnD to produce in each case a 90:10 mixture of exo- and endo-2-deuterionorbornane. The intermediacy of the norbornyl radical was demonstrated by trapping it with the di-*tert*-butylnitrosyl radical (eq. 7.49).



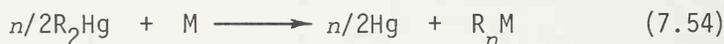
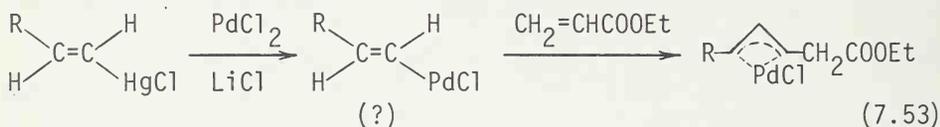
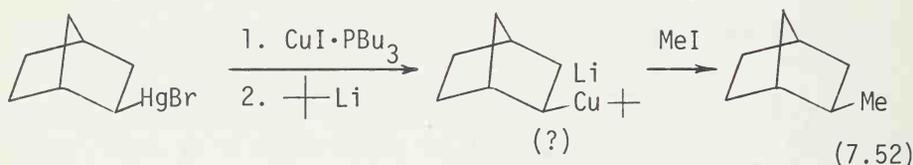
Unlike the reaction of organomercuric halides with NaBH_4 and other metal hydrides, their reaction with Na/Hg appears to be stereospecific (7.42).

7.3.1.4 Transmetallation

Transmetalation represents yet another general mode of cleaving the Hg-C bond. The reaction can be induced by a variety of metal-containing compounds (Method XI) and metals (Method XII), as indicated by the following equations (eqs. 7.50 to 7.54).



This reaction sequence provides an interesting route to phenols (7.43). The following transformations indicate that organomercuries can be converted to organocoppers (7.44) and organopalladiums (7.45).



This oxidative-reductive transmetalation reaction (Sect. 2.12) takes place below 100°C with lithium and sodium. When less reactive metals, such as Mg, Zn, Cd, Al, and Sn, are used, higher temperatures ($>100^\circ\text{C}$) are required.

All reactions discussed above except one are substitution reactions of the Hg-C bond. Organomercuries, however, can undergo other types of reactions as well.

7.3.1.5 Eliminations and Rearrangements

Although α - and β -heterosubstituted organomercuries are obtainable as isolable substances, they can undergo α - and β -elimin-

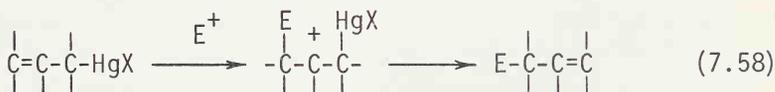
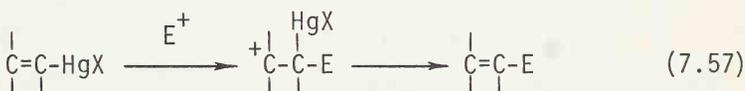
ation reactions, respectively. As discussed later in more detail, certain α -haloorganomercuries produce carbenes on thermolysis (7.11).



β -Heterosubstituted organomercuries can undergo thermal or assisted β -elimination. Thus, for example, β -methoxy organomercuries give olefins on acid treatment, as shown in eq. 7.56 (7.46).



Although we concluded earlier that the intrinsic nucleophilicity of the Hg-C bond is low, α,β - and β,γ -unsaturated organomercuries should be reasonably reactive toward various electrophiles in light of their ability to participate well in the σ - π conjugation (Sect. 6.4.2.1). The carbocationic species produced by such reactions should readily undergo elimination (eqs. 7.57, 7.58).

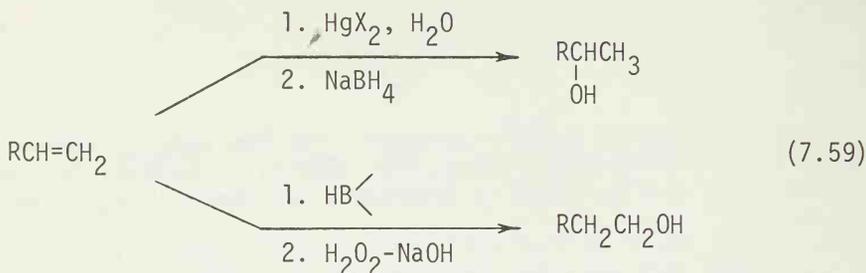


The overall transformation involves substitution of the mercury-containing group with an electrophilic group (E). Although such reaction schemes might prove general and useful, this possibility has not been fully tested. At present few rearrangement reactions involving cleavage of the Hg-C bond are known.

7.3.2 Synthetic Procedures Involving Organomercuries

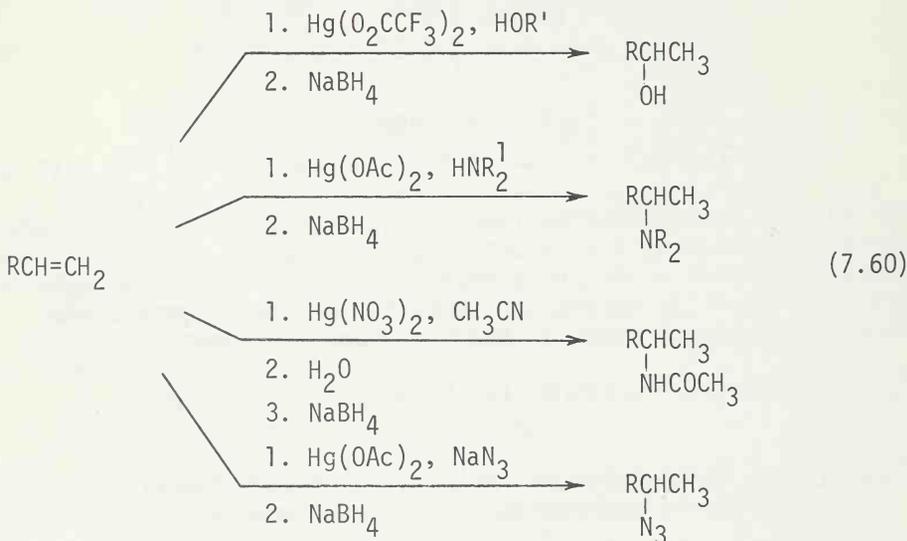
7.3.2.1 The Markovnikov Hydration of Olefins and Related Reactions via Heteromercuriation-Demercuriation

A combination of oxymercuration (Sect. 7.2.2.1) and demercuration by reduction of β -oxyorganomercuries provides one of the most convenient procedures for the Markovnikov hydration of olefins, which nicely complements the anti-Markovnikov hydration via hydroboration-oxidation (eq. 7.59).



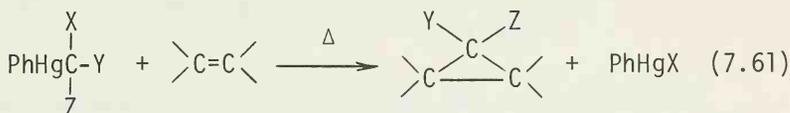
Although in some special cases the reduction of organomercuries with NaBH_4 can be complicated by skeletal rearrangements and other side reactions, it is a highly dependable and general reaction. Thus the scope and limitations of the Markovnikov hydration via oxymercuration-demercuration are roughly comparable to those of the oxymercuration reaction discussed earlier.

Other oxymercuration and heteromercuration reactions can also be combined with the demercuration reaction via reduction with NaBH_4 or other reducing agents to provide convenient procedures for the synthesis of ethers (7.25), amines (7.33), amides (7.34), and azides (7.35), as shown in eq. 7.60.

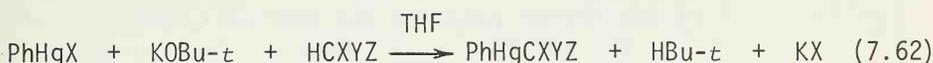


7.3.2.2 Carbene Transfer Reactions

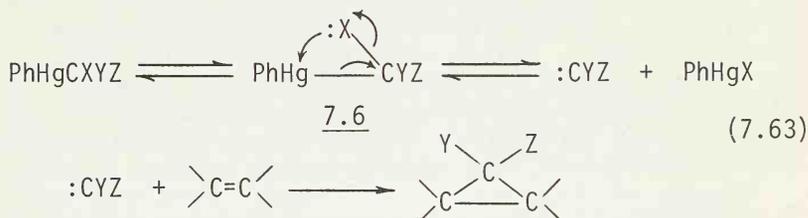
α -Halomethylmercury compounds have been developed as carbene, or divalent carbon, transfer reagents mainly by Seyferth and his associates (7.11).



In many cases the required reagents can be prepared according to the following equation (7.47).

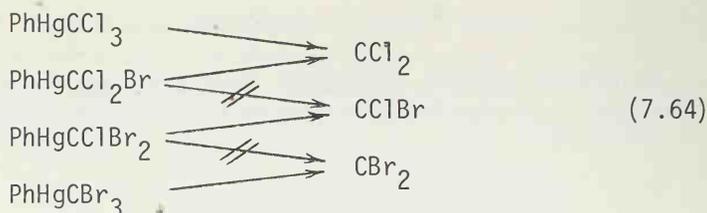


An extensive kinetic and product study by Seyferth (7.11) indicates that in most cases the α -halomethylmercury reagents appear to produce directly free carbenes via 7.6 without involving any carbanion intermediates (eq. 7.63).



In some cases, however, other mechanisms appear to be operating. For example, the reaction of $\text{Hg}(\text{CH}_2\text{Br})_2$ with olefins appears to involve a direct interaction between the two reactants in a manner analogous to the reaction of iodomethylzinc iodide (4.127).

Carbenes or divalent carbon species that have been successfully transferred include: CH_2 , CHCl , CHBr , CF_2 , CCl_2 , CBr_2 , CFCl , CFBr , CClBr , CClCOOR , CBrCOOR , CClSO_2Ph , CBrSO_2Ph , CClSiMe_3 , and CBrSiMe_3 . In accord with the mechanism shown in eq. 7.63, the most nucleophilic and least tightly bound halogen atom is transferred from carbon to mercury, the relative reactivity order of halogens being: $\text{I} > \text{Br} > \text{Cl} > \text{F}$. The relative reactivities of olefins toward phenyl(bromodichloromethyl) mercury are: $\text{Me}_2\text{C}=\text{C}(\text{Me})\text{Et} > \text{Et}_2\text{C}=\text{CHMe} > \text{Pr}(\text{Me})\text{C}=\text{CH}_2 > \text{cyclohexene} > \text{cis-EtCH}=\text{CHPr} > \text{trans-EtCH}=\text{CHPr} > n\text{-C}_5\text{H}_{11}\text{CH}=\text{CH}_2$.



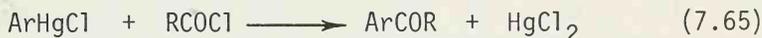
Both the order and the relative rate constants are essentially the same as those observed with CCl_3COONa , indicating that these two reactions involve the same reactive species. One significant difference between the α -halomethylmercury reagents and the more conventional reagents, such as $\text{CHX}_3 + \text{KOBu-}t$ and CX_3COONa , is that the former reagents can produce carbenes thermally and directly, whereas the latter reagents first produce carbanion intermediates ($-\text{CX}_3$), which can induce undesirable side reactions. Although all of these reagents give satisfactory and comparable results in many cases, the α -halomethylmercury reagents are often superior to the more conventional reagents in terms of the product yield. For example, highly electrophilic olefins, such as $\text{CH}_2=\text{CHCN}$ and $\text{CH}_2=\text{CHCOOR}$, may undergo competitive conjugate addition reactions with carbanion intermediates ($-\text{CX}_3$). Such a complication does not appear to exist in the reaction of the α -halomethylmercury reagents. A detailed discussion of the synthetic utility of carbenes is beyond the scope of this monograph. Readers are referred to several extensive monographs on this subject (e.g., 3.11).

7.3.2.3 Other Synthetic Procedures Involving Organomercuries

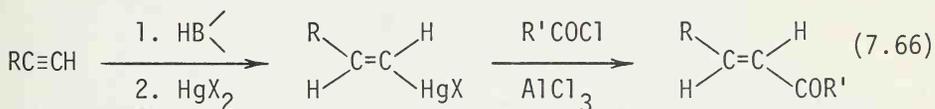
Transmetalation. As discussed earlier (Sect. 7.3.1), organomercuries can be converted via transmetalation into other organometallics, such as those containing Li, Na, Mg, Zn, Cd, B, Al, Sn, Cu, and Pd. These organometallics can, in turn, be utilized in organic synthesis, as discussed in their respective chapters.

Reactions with Carbon Electrophiles. As pointed out earlier (Sect. 7.3.1), unactivated Hg-C bonds are generally inert toward carbon electrophiles. The mercury atom, however, can activate the alkenyl, aryl, and alkynyl groups, which are either directly bonded to or separated by one carbon atom from the mercury atom, through σ - π conjugation. These α,β - and β,γ -unsaturated organomercuries are therefore considerably more reactive toward carbon

electrophiles. Although this property does not appear to have been fully explored and exploited, the following examples point to its potential synthetic utility. Arylmercuric chlorides react with acyl halides to give aryl ketones (7.4).



Alkenylmercuric chlorides and acyl chlorides react at room temperature in the presence of AlCl_3 to give high yields of α, β -unsaturated ketones with retention of configuration (7.4). As a number of alkenylmercuric chlorides can readily be obtained as stereodefined species via hydroboration-transmetalation of acetylenes, the reaction now provides a procedure for the conversion of acetylenes into (E)-alkenyl ketones (eq. 7.66).



7.4 REACTIONS OF ORGANOTHALLIUMS AND ORGANOLEADS

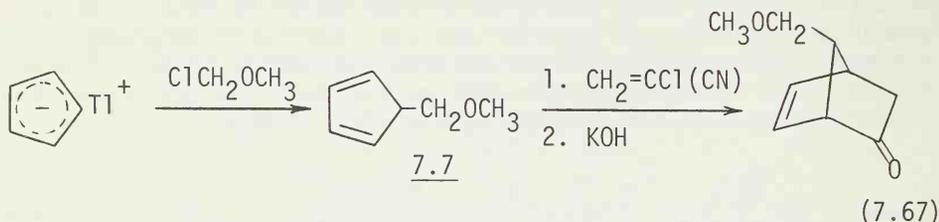
As mentioned in Sect. 7.1.2, organothallium(III) compounds of the R_3Tl and R_2TlX types and organolead(IV) compounds of the R_4Pb , R_3PbX , and R_2PbX_2 types have not found extensive uses in organic synthesis despite their ready availability as isolable species. Also very much limited is the application of organothallium(I) and organolead(II) species in organic synthesis. On the other hand, monoorganothalliums (RTlX_2), which are readily obtainable as unstable intermediates either by thallation of aromatic compounds (Sect. 7.2.3) or by oxythallation of olefins and acetylenes, have exhibited uniquely useful synthetic capabilities. Similarly, in some synthetically useful reactions of olefins and acetylenes with lead(IV) compounds, such as $\text{Pb}(\text{OAc})_4$, monoorganoleads of the RPbX_3 type appear to be formed as unstable intermediates.

7.4.1 Organothalliums in Organic Synthesis

The reactions of organothalliums of current synthetic interest may be classified as follows: (1) alkylation of cyclopentadienylthallium(I), (2) reactions of arylthallium(III) derivatives, and (3) reactions of olefins and acetylenes with thallium(III) salts. There are several excellent reviews on these subjects (7.5, 7.6, 7.48).

7.4.1.1 Organic Synthesis Involving Organothallium(I) Compounds

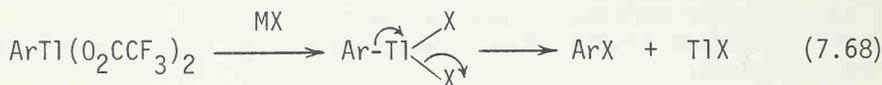
Cyclopentadienylthallium(I) is readily obtainable in 90% yield as a stable organothallium(I) compound by adding freshly distilled cyclopentadiene to a suspension of Tl_2SO_4 in dilute KOH solution (7.49). The potential utility of cyclopentadienylthallium has been demonstrated by its conversion into 5-methoxymethylcyclopentadiene (7.7) which can be further converted to a useful intermediate in the synthesis of the primary prostaglandins (7.50).



Isomerization of 7.7 to 1-methoxymethylcyclopentadiene, which is a serious side reaction in the corresponding reaction of the sodium or lithium salt, does not occur to any significant extent.

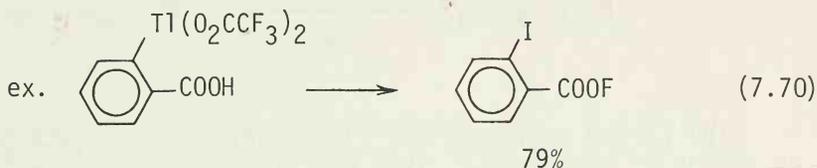
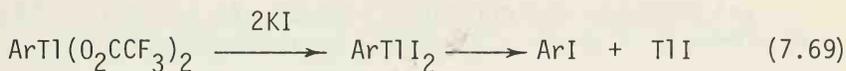
7.4.1.2 Organic Synthesis via Thallation of Aromatic Compounds

Reactions of Arylthalliums with Nucleophiles. As discussed in Sect. 7.2.3, the reaction of arenes with $Tl(O_2CCF_3)_3$ (TTFA) provides a convenient direct entry into arylthalliums of the $ArTlX_2$ type. Although arylthallium difluoroacetates thus obtained are relatively stable, exchange of the O_2CCF_3 group by other groups (X) tends to form unstable derivatives which may decompose to give substituted aromatic compounds. Most of the results can be accommodated by the following general scheme (eq. 7.68).

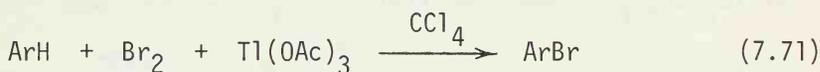


The reaction is regiospecific in that X Group ends up occupying the position originally held by the thallium-containing group. A variety of nucleophiles have been used as the MX reagent.

(a) Halogen nucleophiles. Aryl iodides can readily be prepared using KI (7.51).

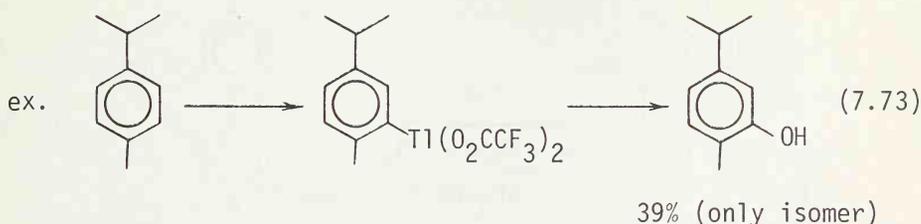
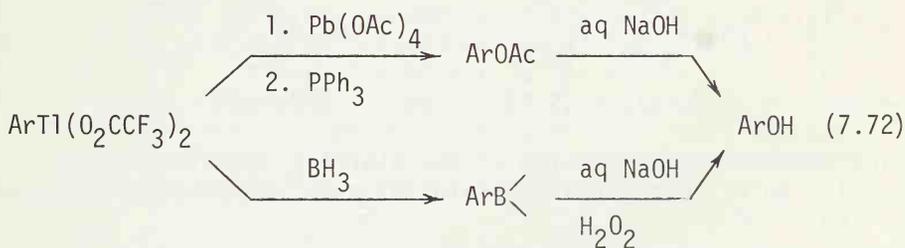


Aryl bromides, on the other hand, can be obtained more directly according to eq. 7.71 (7.52).

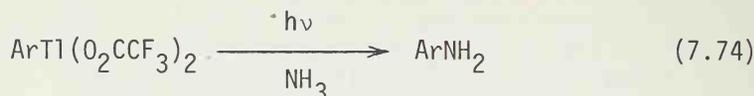


In contrast to the majority of electrophilic aromatic bromination techniques, this procedure usually gives a single, pure monobromo isomer. In the case of monosubstituted benzenes only para bromination takes place. The reaction, however, does not seem to involve the intermediacy of arylthallium species.

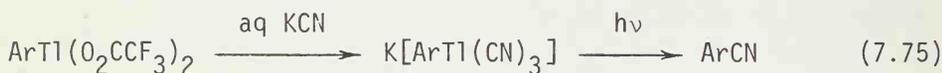
(b) Oxygen nucleophiles. Arylthallium derivatives can be converted to phenols either by treatment with $\text{Pb}(\text{OAc})_4$ and PPh_3 followed by hydrolysis with aqueous NaOH (7.53) or by treatment with a borane reagent followed by oxidation (7.54).



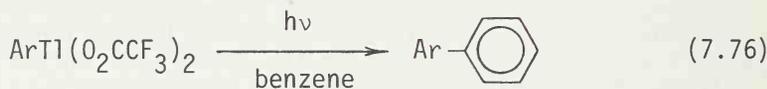
(c) Nitrogen nucleophiles. Photolysis of $\text{ArTl}(\text{O}_2\text{CCF}_3)_2$ in the presence of ammonia gives the corresponding anilines (7.5).



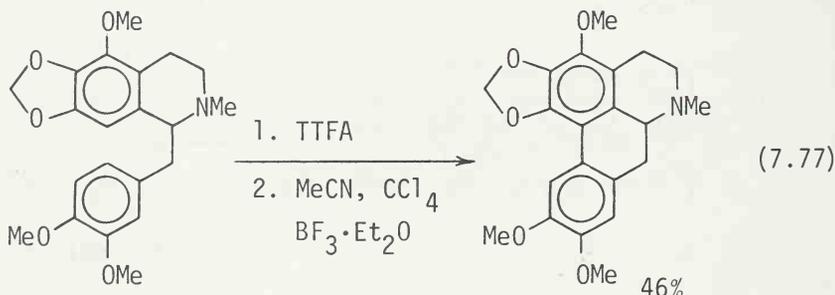
(d) Carbon nucleophiles. Treatment of $\text{ArTl}(\text{O}_2\text{CCF}_3)_2$ with an excess of aqueous KCN gives $\text{K}[\text{ArTl}(\text{CN})_3]$, which can be decomposed by irradiation to form aromatic nitriles (7.53).



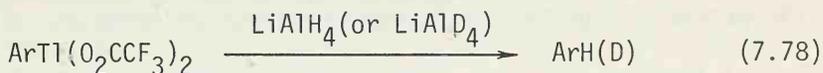
Photolysis of $\text{ArTl}(\text{O}_2\text{CCF}_3)_2$ in benzene produces the corresponding arylated benzenes in high yields (7.55).



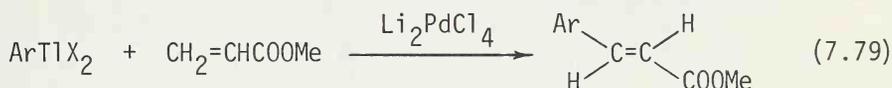
The intramolecular version of the biaryl synthesis provides a facile entry into certain alkaloids, such as ocoteine, as shown in eq. 7.77 (7.56).



(e) Hydrogen nucleophiles. The reaction of $\text{ArTl}(\text{O}_2\text{CCF}_3)_2$ with LiAlH_4 (or LiAlD_4) gives ArH (or ArD) (7.5).



Reactions of Arylthalliums with Electrophiles. Arylthallium compounds are capable of reacting with electrophiles as indicated by their reactions with $\text{Pb}(\text{OAc})_4$ and borane (eq. 7.72). The reaction of arylthalliums with Li_2PdCl_4 in the presence of olefins produces arylated olefins (7.57). The reaction presumably involves formation of arylpalladiums via transmetalation.

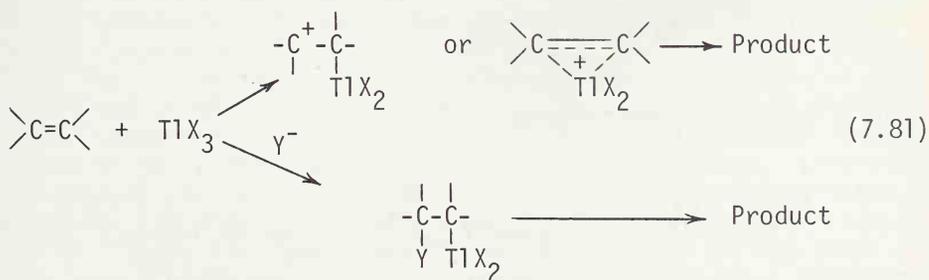


Arylthalliums also react with certain nonmetallic electrophiles. Their reaction with nitrosyl chloride gives nitrosoarenes (7.58).



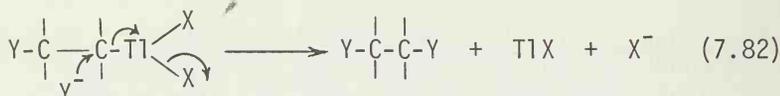
7.4.1.3 Organic Synthesis via Oxythallation

Various thallium(III) salts, such as $\text{Tl}(\text{NO}_3)_3$ (TTN), $\text{Tl}(\text{OAc})_3$, $\text{Tl}(\text{O}_2\text{CCF}_3)_3$ (TTFA), $\text{Tl}_2(\text{SO}_4)_3$, and $\text{Tl}(\text{ClO}_4)_3$, react with olefins acetylenes to form the corresponding monoalkylthallium(III) derivatives (7.5). In marked contrast to the oxymercuration products, however, the monoalkylthallium(III) derivatives are generally quite unstable and decompose spontaneously under the oxythallation conditions in the great majority of cases, although some such derivatives have been isolated.

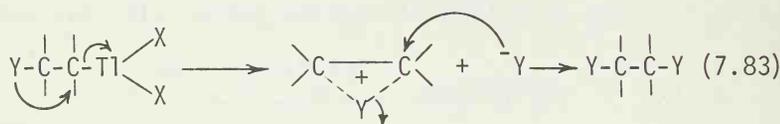


The fate of the monoalkylthallium(III) derivatives depends on a number of factors. The results obtained to date can, however, be interpreted in terms of the following several mechanistic schemes suggested by Taylor and McKillop (7.5b).

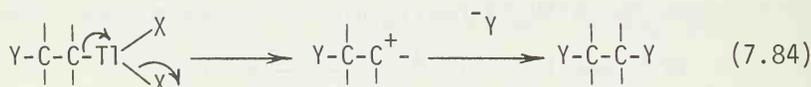
Type 1 (s_N2)



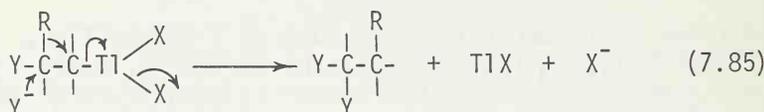
Type 2 (s_Ni)



Type 3 (s_N1)



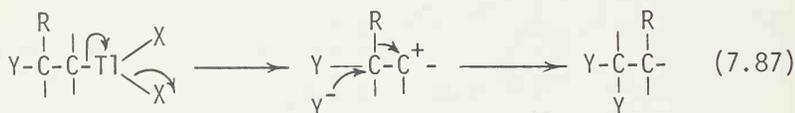
Type 4 (s_N2 with rearrangement)



Type 5 (s_Ni with rearrangement)

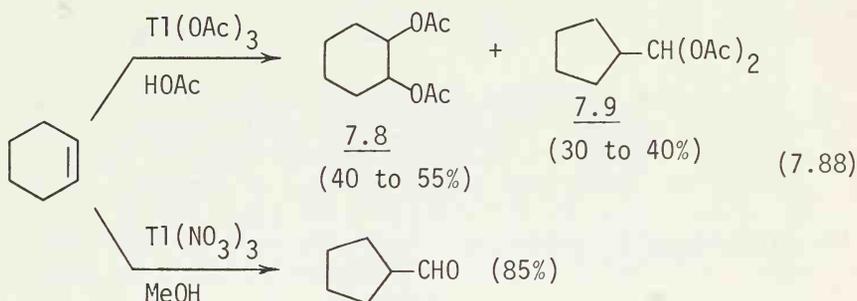


Type 6 (s_N1 with rearrangement)



It should be noted that the first three reactions bring about the same overall transformations and are different only in mechanistic details. Likewise, the Types 4 to 6 reactions involve basically the same overall transformations. Since we are primarily concerned with the synthetic aspects of these reactions, for the sake of convenience the Types 1 to 3 and Types 4 to 6 reactions will be termed the Type A and Type B reactions, respectively. Both Type A and Type B reactions involve reduction of thallium(III) to thallium(I), which proceeds via cleavage of the thermodynamically very weak (25 to 30 kcal/mole) Tl-C bond.

Unfortunately, the exact course of a given reaction is still quite difficult to predict, and is dependent on a number of reaction parameters. Mainly due to the systematic studies by Taylor and McKillop, however, we now can not only readily interpret the observed results but, in many cases, steer these reactions in the desired directions. For example, the reaction of cyclohexene with $\text{Tl}(\text{OAc})_3$ in HOAc was reported to give a mixture of 7.8 and 7.9 along with other minor products (7.59).

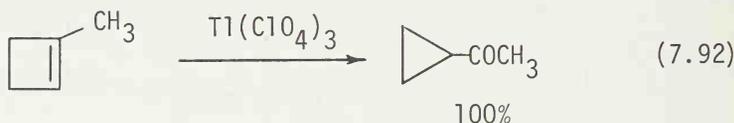
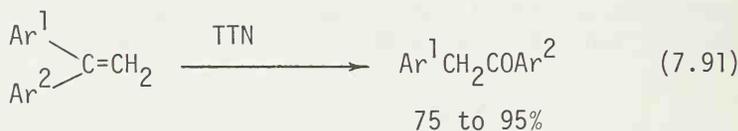
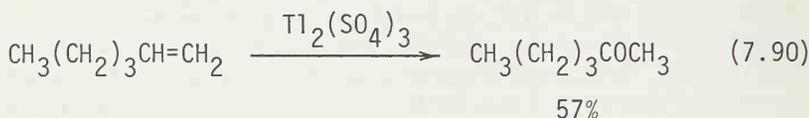
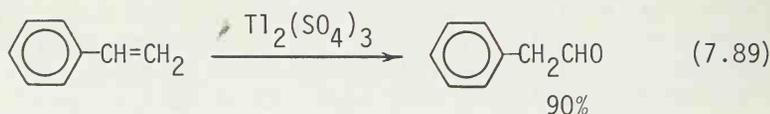


The glycol and acetal derivatives must have arisen via Type A and Type B processes, respectively. If $\text{Tl}(\text{NO}_3)_3$ is used in place of $\text{Tl}(\text{OAc})_3$, the Type B process predominates, producing cyclopentanecarboxaldehyde in 85% yield. Thus the Type B reaction can be favored over the Type A reaction by highly ionic thallium(III) compounds, such as $\text{Tl}(\text{NO}_3)_3$, $\text{Tl}(\text{ClO}_4)_3$, and $\text{Tl}_2(\text{SO}_4)_3$, which contain poor nucleophilic ligands.

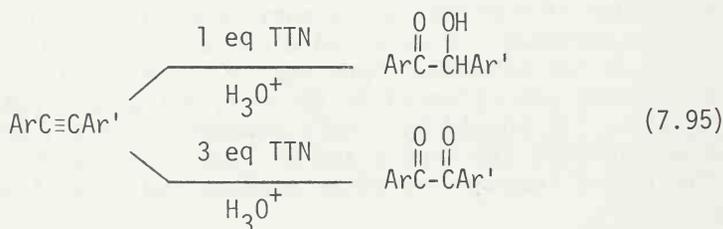
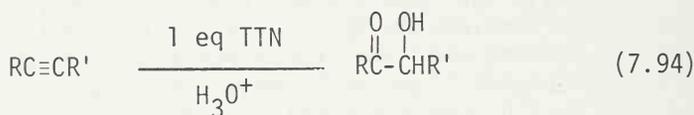
The following examples indicate the synthetic scope of the reactions of olefins, acetylenes, and ketones with such thallium(III) compounds. A detailed discussion of each of these reactions is not presented here due to space limitations. Interested readers are referred to the original papers reporting these results. It should be clear, however, that all of these reactions involve the Type A and/or Type B processes as key steps. The Type B reaction is often accompanied by a skeletal rearrange-

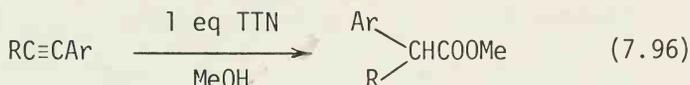
ment, which involves migration of a carbon group. On the other hand, if a hydrogen atom migrates, no skeletal rearrangement results.

1. Olefins (7.60):

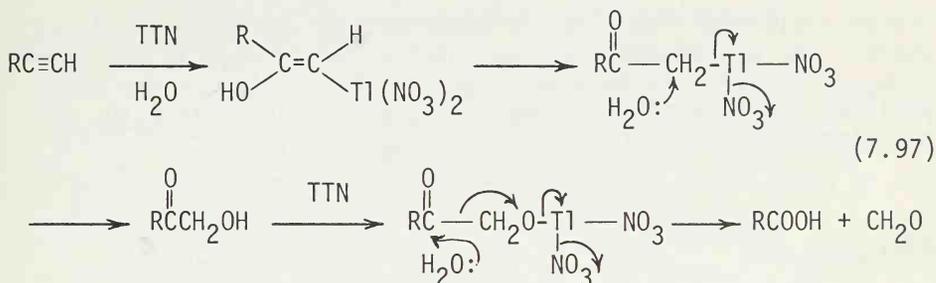


2. Acetylenes (7.61):

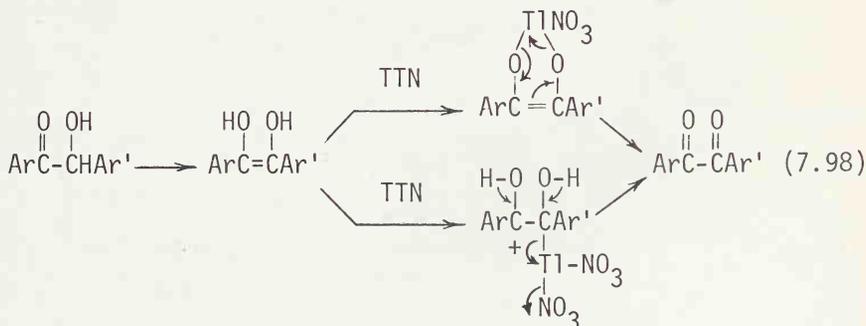




As indicated in the equations above, more than one equivalent of the thallium(III) reagent is required in some cases to observe a complete consumption of the acetylene used. The reaction of monoalkylacetylenes presumably involves a process consisting of oxythallation, tautomerization, Type A reaction, and TTN-promoted fragmentation (eq. 7.97).

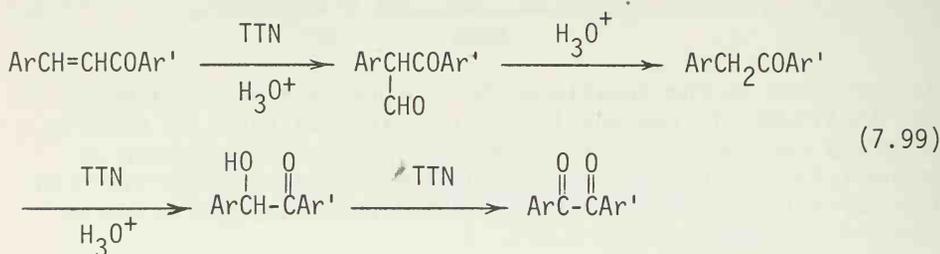


The fragmentation reaction is not competitive in the case of dialkylacetylenes (eq. 7.94). The reaction of monoarylacetylenes does not appear to have been investigated in detail. Benzoin, which can be obtained in varying yields from diarylacetylenes, readily enolize and react further with TTN to form benzils. A cyclic mechanism has been proposed, but the results can also be accommodated by a thallation-dethallation mechanism (eq. 7.98).

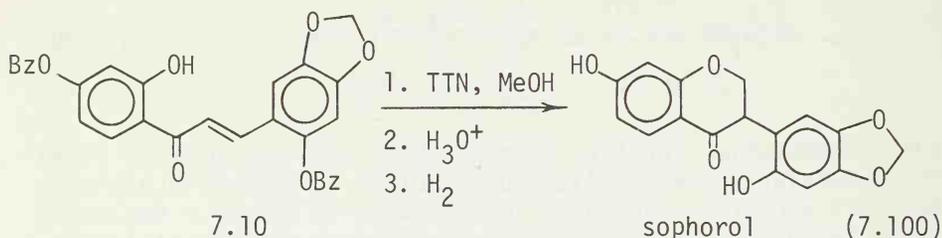


The results obtained with alkylarylacetylenes have been interpreted in terms of a process consisting of oxythallation, Type B reaction, and hydrolysis (7.61).

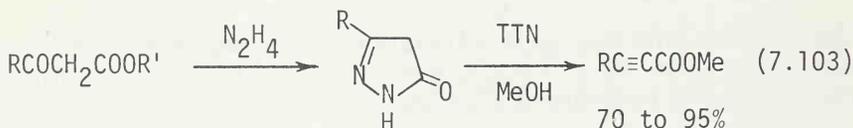
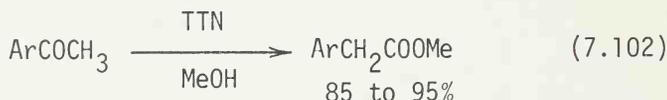
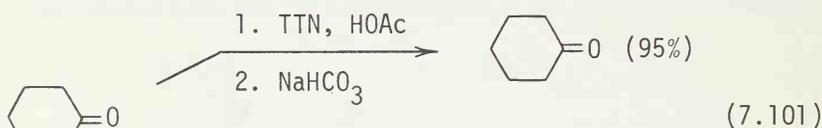
3. Chalcones:

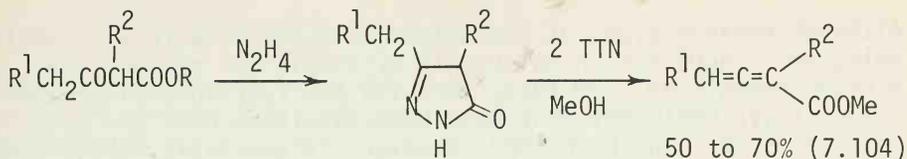


One equivalent of TTN converts chalcones to aryl benzyl ketones, whereas the use of three equivalents of TTN results in the formation of benzils via benzoin (7.62). When chalcones are appropriately substituted with a hydroxy group as shown in 7.10, they can readily be converted to isoflavones (7.63).

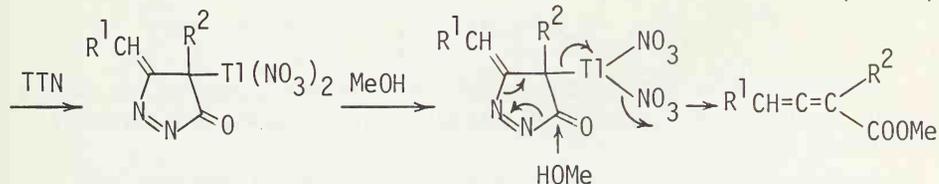
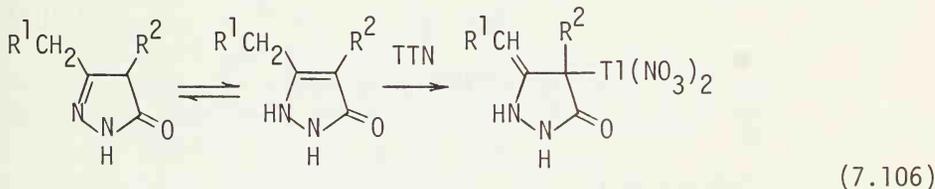
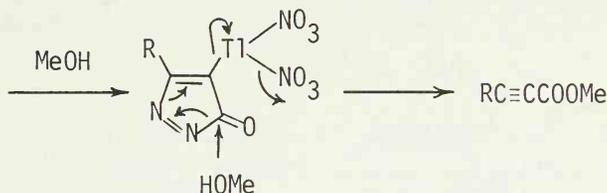
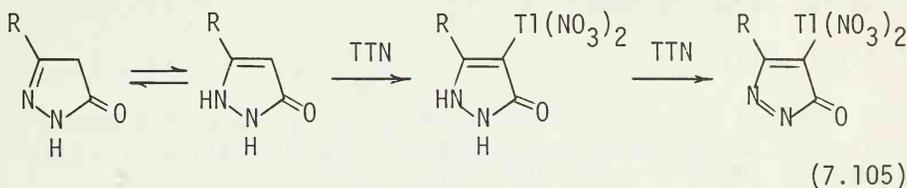


4. Ketones (pyrazolones):





Enols and enamines most probably are the actual reactive species in these reactions. One can think of a number of different mechanistic paths for the reaction shown in eq. 7.101 (7.5). The Willgerodt-like reaction of acetophenones must involve a process consisting of enolization, oxythallation, and Type B reaction (7.64). The following schemes have been proposed for the reactions of pyrazolones (7.65).



The corresponding reactions of aldehydes do not appear to have been well delineated.

7.4.2 Organoleads in Organic Synthesis

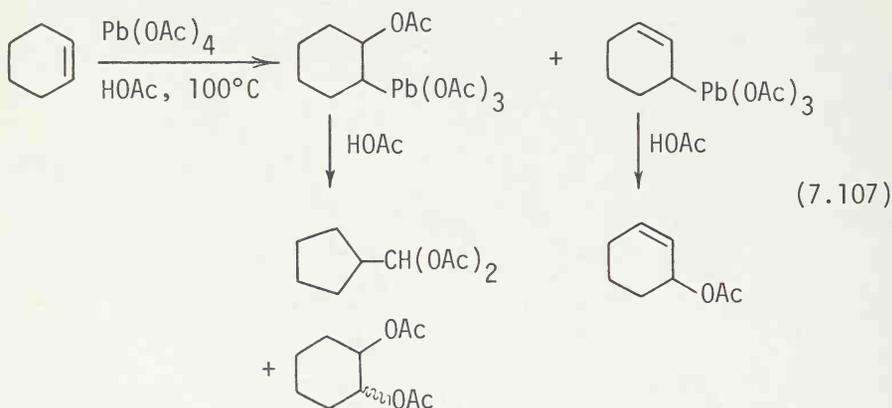
Although various types of organolead compounds are readily available, their application to organic synthesis has not been explored extensively. In fact, very few new reactions of organoleads of synthetic interest have been developed over the past several years. The Pb-C bond, however, is generally labile and reactive. Therefore, organoleads might turn out to be a useful class of reagents and intermediates in the future.

In this section, a few reactions of $\text{Pb}(\text{OAc})_4$ with organic compounds which presumably proceed via unstable monoorganolead derivatives, will be briefly described.

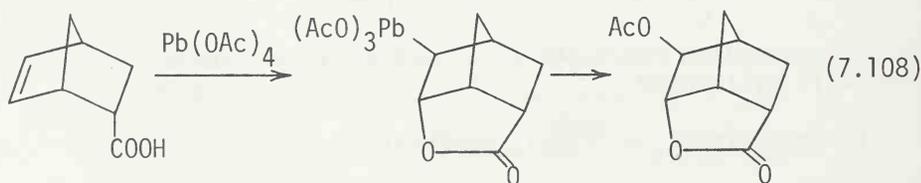
The major driving forces of these reactions are: (a) the high polarizability and instability of the Pb(IV)-O bond, and (b) the ease with which the Pb-C bond is cleaved via one- and/or two-electron reduction (Sect. 7.1.1).

7.4.2.1 Olefins

The reaction of olefins with $\text{Pb}(\text{OAc})_4$ can proceed in a manner analogous to the corresponding reaction with thallium(III) compounds as shown in eq. 7.107 (7.66).

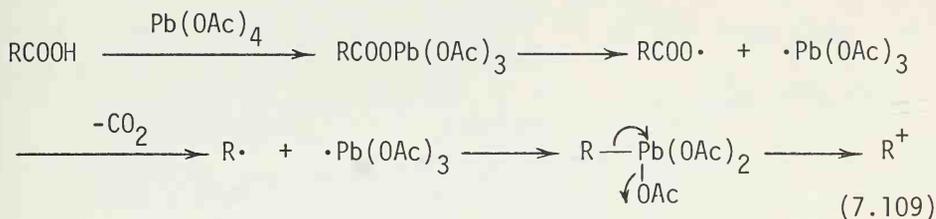


In some favorable cases, the reaction proceeds cleanly, as shown in eq. 7.108 (7.67), although mixtures of products are usually obtained.

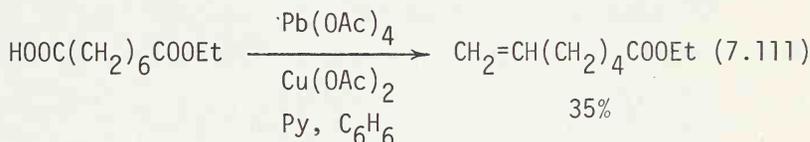
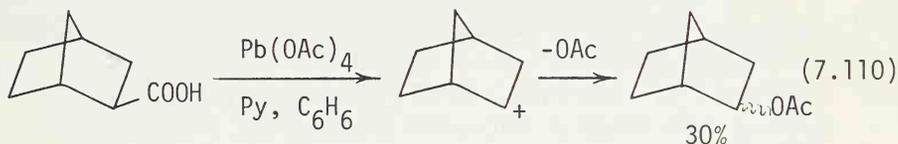


7.4.2.2 Carboxylic Acids

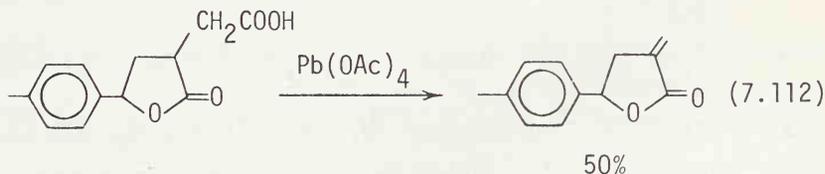
Carboxylic acids can be oxidized with $\text{Pb}(\text{OAc})_4$ to produce decarboxylated carbocations presumably via monoorganolead species. The carbocations thus generated may undergo a variety of reactions characteristic of such species (7.68).



Typical examples follow (7.68).

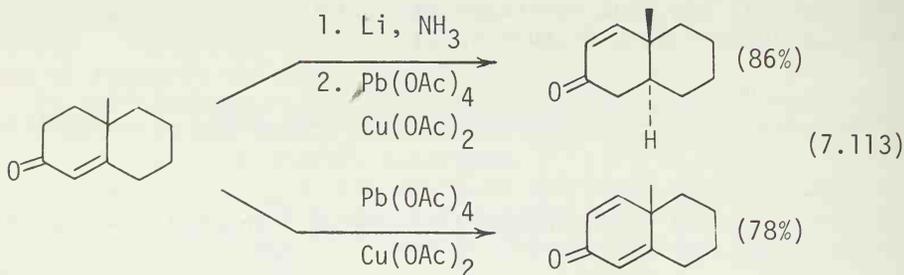


This procedure is applicable to the synthesis of α -methylene-lactones (eq. 7.112) (7.69) and enones (eq. 7.113) (7.70).



The current scope of the use of organoleads in organic synthesis clearly is limited. Their ready availability and high reactivity, however, seem to warrant extensive future investigations in this area. For example, despite the fact that the Pd-C bond can greatly stabilize an adjacent carbocation center through σ - π conjugation (Sect. 6.4.1), little effort appears to have been

made to exploit this attractive capability of lead. Explorations of the reactions of alkenyl-, aryl-, and alkynylleads might prove fruitful.



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Appendix I

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Appendix III

ELECTRONIC CONFIGURATIONS OF THE ELEMENTS

Element	1s	2s	2p	3s	3p	3d	4s	4p	4d
1. H	1								
2. He	2								
3. Li	2	1							
4. Be	2	2							
5. B	2	2	1						
6. C	2	2	2						
7. N	2	2	3						
8. O	2	2	4						
9. F	2	2	5						
10. Ne	2	2	6						
11. Na	2	2	6	1					
12. Mg	2	2	6	2					
13. Al	2	2	6	2	1				
14. Si	2	2	6	2	2				
15. P	2	2	6	2	3				
16. S	2	2	6	2	4				
17. Cl	2	2	6	2	5				
18. Ar	2	2	6	2	6				
19. K	2	2	6	2	6		1		
20. Ca	2	2	6	2	6		2		
21. Sc	2	2	6	2	6	1			
22. Ti	2	2	6	2	6	2			
23. V	2	2	6	2	6	3			
24. Cr	2	2	6	2	6	5	1		
25. Mn	2	2	6	2	6	5	2		
26. Fe	2	2	6	2	6	6	2		
27. Co	2	2	6	2	6	7	2		
28. Ni	2	2	6	2	6	8	2		
29. Cu	2	2	6	2	6	10	1		
30. Zn	2	2	6	2	6	10	2		
31. Ga	2	2	6	2	6	10	2	1	
32. Ge	2	2	6	2	6	10	2	2	
33. As	2	2	6	2	6	10	2	3	
34. Se	2	2	6	2	6	10	2	4	
35. Br	2	2	6	2	6	10	2	5	
36. Kr	2	2	6	2	6	10	2	6	

Element	K	L	M	4s	4p	4d	4f	5s	5p	5d	5f	5g	6s	6p	6d
37. Rb	2	8	18	2	6			1							
38. Sr	2	8	18	2	6			2							
39. Y	2	8	18	2	6	1		2							
40. Zr	2	8	18	2	6	2		2							
41. Nb	2	8	18	2	6	4		1							
42. Mo	2	8	18	2	6	5		1							
43. Tc	2	8	18	2	6	6		1							
44. Ru	2	8	18	2	6	7		1							
45. Rh	2	8	18	2	6	8		1							
46. Pd	2	8	18	2	6	10									
47. Ag	2	8	18	2	6	10		1							
48. Cd	2	8	18	2	6	10		2							
49. In	2	8	18	2	6	10		2	1						
50. Sn	2	8	18	2	6	10		2	2						
51. Sb	2	8	18	2	6	10		2	3						
52. Te	2	8	18	2	6	10		2	4						
53. I	2	8	18	2	6	10		2	5						
54. Xe	2	8	18	2	6	10		2	6						
55. Cs	2	8	18	2	6	10		2	6					1	
56. Ba	2	8	18	2	6	10		2	6					2	
57. La	2	8	18	2	6	10		2	6	1				2	
58. Ce	2	8	18	2	6	10	2	2	6					2	
59. Pr	2	8	18	2	6	10	3	2	6					2	
60. Nd	2	8	18	2	6	10	4	2	6					2	
61. Pm	2	8	18	2	6	10	5	2	6					2	
62. Sm	2	8	18	2	6	10	6	2	6					2	
63. Eu	2	8	18	2	6	10	7	2	6					2	
64. Gd	2	8	18	2	6	10	7	2	6	1				2	
65. Tb	2	8	18	2	6	10	9	2	6					2	
66. Dy	2	8	18	2	6	10	10	2	6					2	
67. Ho	2	8	18	2	6	10	11	2	6					2	
68. Er	2	8	18	2	6	10	12	2	6					2	
69. Tm	2	8	18	2	6	10	13	2	6					2	
70. Yb	2	8	18	2	6	10	14	2	6					2	
71. Lu	2	8	18	2	6	10	14	2	6	1				2	
72. Hf	2	8	18	2	6	10	14	2	6	2				2	
73. Ta	2	8	18	2	6	10	14	2	6	3				2	
74. W	2	8	18	2	6	10	14	2	6	4				2	
75. Re	2	8	18	2	6	10	14	2	6	5				2	
76. Os	2	8	18	2	6	10	14	2	6	6				2	
77. Ir	2	8	18	2	6	10	14	2	6	7				2	
78. Pt	2	8	18	2	6	10	14	2	6	9				1	

Element	K	L	M	4s	4p	4d	4f	5s	5p	5d	5g	6s	6p	6d	7
79.	Au	2	8	18	2	6	10	14	2	6	10			1	
80.	Hg	2	8	18	2	6	10	14	2	6	10			2	
81.	Tl	2	8	18	2	6	10	14	2	6	10			2	1
82.	Pb	2	8	18	2	6	10	14	2	6	10			2	2
83.	Bi	2	8	18	2	6	10	14	2	6	10			2	3
84.	Po	2	8	18	2	6	10	14	2	6	10			2	4
85.	At	2	8	18	2	6	10	14	2	6	10			2	5
86.	Rn	2	8	18	2	6	10	14	2	6	10			2	6
87.	Fr	2	8	18	2	6	10	14	2	6	10			2	6
88.	Ra	2	8	18	2	6	10	14	2	6	10			2	6
89.	Ac	2	8	18	2	6	10	14	2	6	10			2	6
90.	Th	2	8	18	2	6	10	14	2	6	10			2	6
91.	Pa	2	8	18	2	6	10	14	2	6	10	2		2	6
92.	U	2	8	18	2	6	10	14	2	6	10	3		2	6
93.	Np	2	8	18	2	6	10	14	2	6	10	5		2	6
94.	Pu	2	8	18	2	6	10	14	2	6	10	6		2	6
95.	Am	2	8	18	2	6	10	14	2	6	10	7		2	6
96.	Cm	2	8	18	2	6	10	14	2	6	10	7		2	6
97.	Bk	2	8	18	2	6	10	14	2	6	10	8		2	6
98.	Cf	2	8	18	2	6	10	14	2	6	10	10		2	6
99.	Es	2	8	18	2	6	10	14	2	6	10	11		2	6
100.	Fm	2	8	18	2	6	10	14	2	6	10	12		2	6
101.	Md	2	8	18	2	6	10	14	2	6	10	13		2	6
102.	-	2	8	18	2	6	10	14	2	6	10	14		2	6
103.	Lw	2	8	18	2	6	10	14	2	6	10	14		2	6

Appendix IV

IONIZATION ENERGIES^a

Element	Ionization Energies (eV)			Element	Ionization Energies (eV)		
	I	II	III		I	II	III
H	13.60			Ru	7.37	16.76	28.47
He	24.59	54.42		Rh	7.46	18.08	31.06
Li	5.39	75.64	122.45	Pd	8.34	19.43	32.93
Be	9.32	18.21	153.89	Ag	7.58	21.49	34.83
B	8.30	25.15	37.93	Cd	8.99	16.91	37.48
C	11.26	24.38	47.89	In	5.79	18.87	28.03
N	14.53	29.60	47.45	Sn	7.34	14.63	30.50
O	13.62	35.12	54.93	Sb	8.64	16.53	25.3
F	17.42	34.97	62.71	Te	9.01	18.06	27.96
Ne	21.56	40.96	63.45	I	10.45	19.13	33.00
Na	5.14	47.29	71.64	Xe	12.13	21.21	32.1
Mg	7.65	15.04	80.14	Cs	3.89	23.1	
Al	5.99	18.83	28.45	Ba	5.21	10.00	
Si	8.15	16.34	34.49	La	5.58	11.06	19.18
P	10.49	19.72	30.18	Ce	5.47	10.85	20.20
S	10.36	23.33	34.83	Pr	5.42	10.55	21.62
Cl	12.97	23.81	39.61	Nd	5.49	10.72	
Ar	15.76	27.63	40.74	Pm	5.55	10.90	
K	4.34	31.62	45.72	Sm	5.63	11.07	
Ca	6.11	11.87	50.91	Eu	5.67	11.25	
Sc	6.54	12.80	24.76	Gd	6.13	12.1	
Ti	6.82	13.58	27.49	Tb	5.85	11.52	
V	6.74	14.65	29.31	Dy	5.93	11.67	
Cr	6.77	15.50	30.96	Ho	6.02	11.80	
Mn	7.44	15.64	33.67	Er	6.10	11.93	
Fe	7.87	16.18	30.65	Tm	6.18	12.05	23.71
Co	7.86	17.06	33.50	Yb	6.25	12.17	25.2
Ni	7.64	18.17	35.17	Lu	5.43	13.9	
Cu	7.73	20.29	36.83	Hf	7.0	14.9	23.3
Zn	9.39	17.96	39.72	Ta	7.89		
Ga	6.00	20.51	30.71	W	7.98		
Ge	7.90	15.93	34.22	Re	7.88		
As	9.81	18.63	28.35	Os	8.7		
Se	9.75	21.19	30.82	Ir	9.1		
Br	11.81	21.08	36.00	Pt	9.0	15.56	
Kr	14.00	24.36	36.95	Au	9.22	20.5	
Rb	4.18	27.28	40.00	Hg	10.44	18.76	34.2
Sr	5.70	11.03	43.06	Tl	6.11	20.43	29.83
Y	6.38	12.24	20.52	Pb	7.42	15.03	31.94
Zn	6.84	13.13	22.99	Bi	7.29	16.69	25.56
Nb	6.88	14.32	25.04	Po	8.42		
Mo	7.10	16.15	27.16	At			
Tc	7.28	15.26	29.54	Rn	10.75		

^a The ionization energy values are taken from Moore, C. E., *Ionization Potentials and Ionization Limits Derived from the Analyses of Optical Spectra*, NSRDS-NBS 34, National Bureau of Standards, Washington, D. C., 1970. Most of the values cited in this table are rounded to the nearest hundredth.

Appendix V

COVALENT AND IONIC RADII (Å)^a

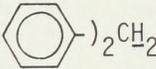
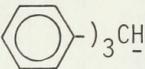
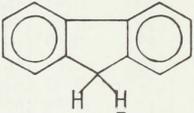
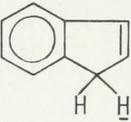
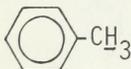
Element	V_{cov}	V_{ion}	Element	V_{cov}	V_{ion}
H	0.37	2.08 (-1)	Rb	2.16	1.48 (+1)
Li	1.34	0.64 (+1)	Sr	1.91	1.13 (+2)
Be	1.25	0.31 (+2)	Y	1.62	0.93 (+3)
B	0.90	0.20 (+3)	Zr	1.45	0.80 (+4)
C	0.77	2.60 (-4)	Nb	1.34	0.70 (+5)
N	0.75	1.71 (-3)	Mo	1.30	0.62 (+6)
O	0.73	1.40 (-2)	Tc	1.27	0.63 (+4)
F	0.71	1.36 (-1)	Ru	1.25	0.62 to 0.70
Na	1.54	0.95 (+1)	Rh	1.25	0.62 to 0.67
Mg	1.45	0.65 (+2)	Pd	1.28	0.64 to 0.86
Al	1.30	0.50 (+3)	Ag	1.34	1.26 (+1)
Si	1.18	0.41 (+4)	Cd	1.48	0.97 (+2)
P	1.10	2.12 (-2)	In	1.44	0.81 (+3)
S	1.02	1.82 (-2)	Sn	1.40	0.71 (+4)
Cl	0.99	1.81 (-1)	Sb	1.43	0.62 (+5)
K	1.96	1.33 (+1)	Te	1.35	2.21 (-2)
Ca	1.74	0.99 (+2)	I	1.33	2.16 (-1)
Sc	1.44	0.81 (+3)	Cs	2.35	1.69 (+1)
Ti	1.32	0.68 (+4)	Ba	1.98	1.35 (+2)
V	1.22	0.59 (+5)	La	1.69	1.18 (+3)
Cr	1.18	0.52 (+6)	Hf	1.44	0.71 to 0.83 (+4)
Mn	1.17	0.46 (+7)	Ta	1.34	0.64 to 0.67
Fe	1.17	0.49 to 0.78	W	1.30	0.41 to 0.65
Co	1.16	0.53 to 0.74	Re	1.28	0.40 to 0.63
Ni	1.16	0.56 to 0.70	Os	1.26	0.63 (+4)
Cu	1.17	0.96 (+1)	Ir	1.27	0.63 to 0.73
Zn	1.25	0.74 (+2)	Pt	1.30	0.60 to 0.99
Ga	1.26	0.62 (+3)	Au	1.34	1.37 (+1)
Ge	1.22	0.53 (+4)	Hg	1.49	1.10 (+2)
As	1.22	0.47 (+5)	Tl	1.48	0.95 (+3)
Se	1.17	0.42 (+6)	Pb	1.47	0.78 to 0.94 (+4)
Br	1.14	0.39 (+7)			

^a The covalent and ionic radii listed in this table are taken from Huheey, J. E., *Inorganic Chemistry*, Harper & Row, New York, 1972, pp. 73 to 75, 184 to 185, and from *Table of Periodic Properties of the Elements* (Catalog No. S-18806). Sargent-Welch Scientific Co., Skokie, Ill.

Appendix VI

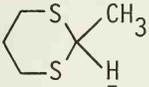
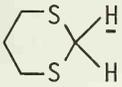
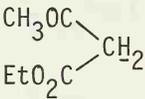
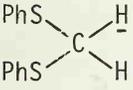
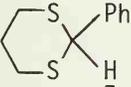
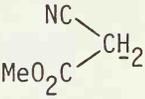
ACIDITY OF BRONSTED ACIDS

Table 1. Hydrocarbon Acids ^a

Compound	pK _a	Compound	pK _a
t-Bu-H	> 52		34
	51 to 52		31.5
Et-H	49 to 50	HC≡CH	25
	46		23
H ₂ C=CH ₂	44		19 to 20
	43		15 to 16
	41		
H ₂ C=CHCH ₃	40		

^a These pK_a values are taken from: Streitwieser, A., Jr., and Heathcock, C.H., *Introduction to Organic Chemistry*, Macmillan, New York, 1976, 1279 pp.

Table 2. Hetero-Substituted Carbon Acids ^a

Compound	pK _a	Compound	pK _a
	38 ^b	(CH ₃ SO ₂) ₂ CH ₂	14
PhSOCH ₃	35 ^c	(NC) ₂ CH ₂	11
	31 ^b		11
	31 ^d	O ₂ NCH ₃	10
	29 ^b	NCH ₃	9
RSO ₂ CH ₃	23 to 27 ^c	(CH ₃ OC) ₂ CH ₂	9
NCCH ₃	25		9
Cl ₃ CH	25	(CH ₃ OC) ₃ CH	5.9
EtO ₂ CCH ₃	24 to 25	(O ₂ N) ₂ CH ₂	3.6
CH ₃ COCH ₃	20	(O ₂ N) ₃ CH	0
		SNCH ₃	-1.9

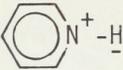
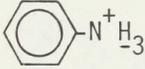
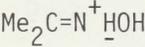
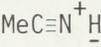
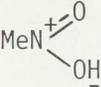
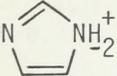
^a Unless otherwise noted, the pK_a values are taken from the reference cited in footnote ^a of Table 1.

^b Streitwieser, A., Jr., and Ewig, S. P., *J. Am. Chem. Soc.*, 97, 190 (1975).

^c House, H. O., *Modern Synthetic Reactions*, 2nd ed., W. A., Benjamin, Menlo Park, Calif., 1972, p. 494. Bordwell, F. G., Mathews, W. S., Vanier, N. R., *J. Am. Chem. Soc.*, 97, 442 (1975).

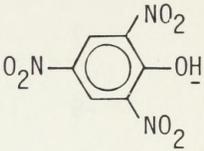
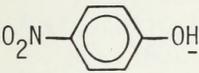
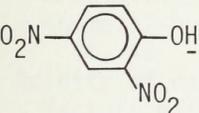
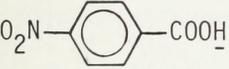
^d Bordwell, F. G., and Mathews, W. S., *J. Am. Chem. Soc.*, 96, 1214 (1974).

Table 3. Amines and Other Nitrogen Acids ^a

Compound	pK _a	Compound	pK _a
MeNH ₂	35		5.3
NH ₃	35		4.6
PhNH ₂	27 ^b		1.0
Ph ₂ NH	23 ^b		-1.9
Me ₂ N ⁺ H ₂	11		-10
MeN ⁺ H ₃	10.6		-12
Me ₃ N ⁺ H	10		
N ⁺ H ₄	9.2		
	7.0		

^a See footnote a of Table 2.
^b Hendrickson, J. B., Cram, D. J., and Hammond, G. S., *Organic Chemistry*, 3rd ed., McGraw-Hill, New York, 1970, p. 304.

Table 4. Oxygen Acids ^a

Compound	pK _a	Compound	pK _a
<i>t</i> -BuOH ₋	18	O ₃ NH ₋	1.3
EtOH ₋	16		0.25
OH ₋₂	15.7	CF ₃ COOH ₋	0.2
O ₂ H ₋₂	11.6	Me ₂ S ⁺ OH ₋	0
PhOH ₋	10	CH ₄ SO ₃ H ₋	-1.2
O ₃ BH ₋₃	9.2	EtO ⁺ H ₋₂	-2.4
BrOH ₋	8.6	<i>t</i> -BuO ⁺ H ₋₂	-3.8
ClOH ₋	7.5	O ₄ SH ₋₂	-5.2
	7.2	CH ₃ C=O ⁺ H ₋ OEt	-6.5
O ₃ CH ₋₂	6.4	PhO ⁺ H ₋ CH ₃	-6.5
CH ₃ COOH ₋	4.7	PhO ⁺ H ₋₂	-6.7
	4.1	Me ₂ C=O ⁺ H ₋	-7
	3.4	MeCH=O ⁺ H ₋	-8
O ₂ NH ₋	3.2	O ₄ ClH ₋	-10
O ₃ PH ₋₃	2.2	MeN ⁺ O(OH ₋)	-12
O ₃ SH ₋₂	1.8		

^a See footnote a of Table 2.

Table 5. Other Acids ^a

Compound	pK _a	Compound	pK _a
FH	3.2	SH ₂	7
ClH	-7	Me ₂ S ⁺ H	-5.2 ^b
BrH	-9		
IH	-9.5	MeS ⁺ H ₂	-7

^a See footnote a of Table 2.

^b See footnote b of Table 3.

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